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Ultrasound Technology And Biomaterials For Precise Drug Therapy

Rakan Saleh Alkhalifah[1] , Emad Abdullah Alrasheed[2] , Khalid obaid alharbi[3] , Hamad ali alruqaibah[4] , Rashed Abdulaziz Alkharfi[5]

[1-5]Radiology technologist.

Abstract:

Advanced ultrasound technology and functional biomaterials can be used to achieve precision drug therapy in different aspects such as dose, space, and/or time. At present, many physical or chemical technologies and preparations, such as ultrasound, light, magnetism, and enzyme, have been used to prepare a variety of functional biomaterials and trigger precise drug delivery. Notably, ultrasound provides a convenient and robust technology for drug triggering and precision therapy and is increasingly being studied and applied. At present, the ultrasound system mainly triggers and realizes precise drug treatment through sonophoresis and sonoopermeation (including inorganic-based nanoparticles, microbubbles, nanobubbles, liposomes, micelles, micro-nanomotors, etc.). This review first introduces the classification of ultrasound and related physical properties involving precision drug treatment, and then systematically discusses the realization of drug precision treatment through sonophoresis and sonopermeation. In particular, key information such as effective ultrasonic intensity and frequency parameter range, types of loaded drugs, systematic therapeutic effect, and so on for precision therapy with an advanced combination of ultrasonic technology and various biological materials were expounded and summarized. In addition, relevant clinical opportunities and challenges are described. Finally, the development and application of ultrasound-functional biomaterials for drug precision therapy are prospected.

Keywords: Ultrasound; Biomaterials; Drug delivery; Controlled release; Precision therapy.

Introduction

Various technologies and advanced functional biomaterial systems can significantly improve the effectiveness of drug precision therapy. At present, these technologies mainly include physical and chemical technologies. Physical technology mainly includes external signals, such as light, magnetic field, electricity, (Asadi et al.2021). However, the physical precision therapy system combined with optical technology and biological materials has many defects, such as poor tissue transmittance, difficult non-invasive treatment, poor biocompatibility, and so on. The clinical safety of electronic and magnetic technologies remains controversial, and customized equipment can be complex and expensive (Durham et al., 2021). In addition, chemically-based stimulant reaction agents mainly include pH, ATP, and enzymes. However, these biomaterial-based precision chemotherapy systems still have some limitations. At present, the use of ATP and PH as drug delivery triggers is mostly in the proof-of-principle stage, and the specificity and immunogenicity of the system still need to be improved • (Fix et al., 2019). Enzymes are difficult to trigger conventional synthetic polymers, and their practical applications and risks need to be further evaluated. Multi-enzyme-mediated cascades are also difficult to achieve. Therefore, the current technology based on physics and chemistry still has many defects, and it is difficult to effectively combine biological materials to achieve accurate delivery of various drugs and the treatment of various diseases (Zhang et al., 2018).

As a non-invasive precision medicine method, ultrasonic technology combined with biological materials within the range of 0 kHz–50 MHz has attracted great attention and has been widely used in the medical field (Liu et al., 2020). As an ideal precision drug therapy system, ultrasound functional biomaterials are closely related to a series of biological and physical effects of ultrasound technology, (Daftardar et al., 2020). Ultrasound can induce cavitations. Many compressible objects, such as nanobubbles and microbubbles, can contract, expand, and rupture during refinement cycles and ultrasonic compression. In addition, the acoustic radiation force refers to the physical phenomenon in which momentum is transferred to the transmission medium in the process of ultrasonic propagation. Particle displacement and fluid flow caused by acoustic radiation force are called “acoustic streaming (T. Manouras, 2017).

Ultrasound classification for precise drug therapy

Ultrasound has been widely concerned in various research and applications. Ultrasound is generally defined as sound waves with frequencies exceeding 2000 Hz. Ultrasound has the characteristics of large penetration depth and fast propagation speed, so it is considered to have a wide range of research and application prospects. Ultrasound, historically, was and is accepted as an effective approach to both diagnostic imaging and physical therapy in clinics. As a novel non-invasive tool, the intensity of ultrasound differs making a clear classification of ultrasound applications in surgery, diagnosis, and therapy. More specifically, the intensity of the diagnostic ultrasound varies from 0.0001to 0.5 W/cm^2 while the intensities of therapeutic ultrasound range from 0.5 to 3 W/cm^2. However, the intensity range of surgical application is usually higher than 10 W/cm (Mitchell et al., 2020).

Ultrasound-related physical properties and characteristics

As ultrasound travels through tissues in the body, several physical effects can be used to trigger drug transdermal delivery directly or in combination with ultrasound to trigger drug release mediated by biomaterials. Relevant physical effects include acoustic fluid flow, simple pressure changes, localized hyperthermia, and cavitation (Paunovska et al., 2021). These related physical properties regulate the triggered delivery of drugs from multiple perspectives and have important practical significance.

Cavitation

Ultrasonic cavitation generally refers to the dynamic growth and rupture process of cavitation bubbles in the liquid gas core when the sound pressure reaches a certain value under the action of sound waves. Ultrasonic propagation in the liquid medium can produce a large amount of sound pressure, when the negative sound pressure generated by this process exceeds the cohesion of the liquid, small holes will appear in the liquid, that is cavitation (Sun et al., 2021).

Acoustic radiation force and acoustic streaming

The stable and time-averaged force generated by the sound field in the process of transferring momentum to the object is called acoustic radiation force. Acoustic radiation force can induce shear stress to open cell connections, thereby increasing cell permeability and improving penetration into dense tissues. The acoustic radiation force causes local fluid flow and particle displacement, which is called“ acoustic streaming ” (Liu et al., 2020). Acoustic streaming can change the distribution of calcium and potassium on both sides of the cell membrane, change the permeability of the cell membrane to substances, and relieve pain by acting on nerve electrical activity. Changes in acoustic streaming can produce a series of physical phenomena such as luminescence, high heat, temporary microbubbles, electrical discharge, bubble bursting, and high pressure, and ultimately regulate various physiological activities of the body (Daftardar et al 2020). Therefore, acoustic streaming can be used as another cavitation effect, which can permeabilize the endothelial cells of the tube, change the stability of the drug carrier, generate different shear stress, and penetrate the cell membrane to increase the local drug transfer coefficient to different degrees (Deprez et al., 2021).

Ultrasound triggers transdermal drug delivery (Sonophoresis)

Sonophoresis refers to the application of high-frequency or low-frequency ultrasound for skin penetration to improve the transdermal absorption of drugs (Bahutair et al 2022). The stratum corneum acts as a natural barrier to the outer structure of the skin but also prevents the transdermal delivery of many drugs. At present, to improve the ability of various drugs to penetrate the skin accurately and deliver, many chemical enhancers are widely used. However, toxic effects and skin irritation symptoms often limit drug transdermal delivery. To alleviate these defects, convenient, safe, and efficient methods to achieve precise drug treatment are urgently needed by researchers. The operation of sonophoresis, although not fully understood, is thought to result from cavitation, although thermal effects cannot be completely ignored (Mitchell et al., 2021).

Ultrasound-functional inorganic-based nanoparticles for drug precision therapy

The widespread use of inorganic-based nanoparticles has brought exciting effects to ultrasonic-functional biomaterial-triggered precision drug therapy. They deliver high concentrations of drugs precisely to diseased organs and tissues and reduce the side effects of drugs. Currently, diagnostic ultrasound has traditionally played an important role in detecting the precise delivery of inorganic nanoparticle-loaded drugs. In addition, they have the advantage of being focused on the target tissue and being non-invasive. Ultrasound can also release various drugs from the inorganic-based nanoparticles and significantly increase the permeability of cell membranes (Paunovska et al., 2022).

Ultrasound-functional liposomes for drug precision therapy

The fusion of liposomes and ultrasound to trigger drug delivery has been extensively studied. As a classic ultrasound-responsive material, liposomes have effectively triggered the delivery of doxorubicin, model drugs, reactive oxygen species, etc., and have been used in a variety of animal and disease models (Fix et al., 2019).

Ultrasound-functional microbubbles for drug precision therapy

In addition to its application as an ultrasound diagnostic contrast agent, microbubbles have also been shown to be an effective drug-targeted delivery technology (Zhang et al., 2018) . Microbubbles can be integrated with drugs in a variety of ways, including specific ligand-site binding and direct complexation of the microbubble shell with the drug.

Ultrasound-functionalized microbubbles are an important innovative way to achieve precise drug treatment in different tissues. Microbubbles are used to carry drugs until they reach a specific area of interest. The microbubbles oscillate when the ultrasonic operating conditions are close to or directly at the resonant frequency. If the ultrasonic pressure is higher, the amplitude oscillation will be higher and lead to many microbubbles' destruction. Utilizing this effect can transiently and locally increase the permeability of various barriers such as capillaries and cell membranes (Zhao et al., 2021).

Ultrasound enhancer

Microbubbles are usually composed of protein or phospholipid-stabilized shells and perfluorocarbon gas cores, which can not only effectively improve the contrast of ultrasonographic images but also enable efficient ultrasound therapy (Gao et al., 2019). Currently, the strong backscattering properties of microbubbles allow for significantly enhanced contrast in ultrasound images. Under low sound pressure, it can stabilize oscillation and produce an echo, which can be used for harmonic ultrasonic imaging and improve the image quality of ultrasonic detection. In addition, some microbubbles have been fully validated clinically and approved for marketing (Zhang et al., 2018).

Ultrasound-functional nanobubbles for drug precision therapy

Nanobubbles are nano-sized carriers. Nanobubbles (usually 150–500 nm in diameter) are submicron-sized microbubbles being effective systems for drug delivery and precision therapy because they can selectively target organs and tissue sites , (Deirram et al., 2019). Compared with microbubbles, nanobubbles are more attractive carriers for precision drug therapy because of their further stability and aggregation.

In traditional applications, nanobubbles are commonly used to enhance the imaging effect of ultrasound and have more and more important diagnostic application value. Nanobubbles can also be applicated for interventional therapy of various organs. More recently, they have also been used to trigger the delivery of drugs (Liu et al., 2020).

Ultrasound-functional multiple materials for drug precision therapy

a variety of responsive biomaterials such as nanoparticles, liposomes, microbubbles, nanobubbles, etc. have been combined with ultrasound and played an important role in many fields. However, a single acoustic-responsive material may not exhibit an excellent effect of triggering drug delivery, and it is necessary to combine two or even multiple biomaterials for synergistic delivery for therapeutic purposes.

(Gao et al.2021) described the preparation of microbubble-liposome complexes of irinotecan and oxaliplatin. The efficacy of microbubble-liposome complexes following sonodynamic therapy was determined in a human pancreatic cancer xenograft mouse model. The results showed that tumors treated with the complex and ultrasound were 136 percent smaller than those treated with the same concentrations of irinotecan/oxaliplatin. (Prabhakar et al. 2022).

Clinical challenges of ultrasound-functional biomaterials for drug precision therapy

The difficulty of real-time temperature monitoring

While the hyperthermic or cavitation effects of ultrasound can rapidly and reversibly increase skin permeability, it can potentially cause damage to skin structures. Higher frequencies cause higher heat to the tissue, which can lead to peripheral burns and exfoliation of the skin. High-intensity and long-duration ultrasound are usually required to generate thermal effects (Bahutair et al. 2022).

Limitations of drugs delivery of organ

Scattered or reflected ultrasound energy may damage internal organs adjacent to the target volume. For example, sciatic nerve injury has been observed following uterine ultrasound treatment. Tissues such as the digestive tract and lungs are not suitable for ultrasound-functionalized biomaterials to trigger drug delivery due to the presence of potential cavities and gases that can exacerbate cavitation. In addition, there may be some air bubbles and gas in the skin, and researchers are concerned that ultrasonic triggering may lead to skin damage and some complications (Daftardar et al.2020).

Difficulty of clinical translation

Numerous basic experiments have confirmed that the drug-based precision therapy of ultrasound-functionalized biomaterials is a potential therapeutic tool in small animal models (Zhang et al.,2018). For acoustic drug delivery, ultrasound can induce differential drug release in cells or tissues, which often requires higher ultrasound energy. Ultrasound-mediated tissue damage is a very important biosafety issue when gene transduction systems need to be applied , The long-term side effects/toxicity of nanocarriers is unknown. Living cells can take up a variety of nanocarriers (Zhao et al., 2021).

Recommendations:

According to the above-mentioned theoretical basis, systematic research, and pre-clinical experiments, the application of ultrasonic functional biomaterials can improve the delivery of various drugs to the disease sites, and achieve precise drug treatment. However, even the ultrasound functional biomaterials have made great progress in delivering precision medicine in recent decades (Deirram et al.,2019). breakthroughs are still needed to effectively address the current shortcomings of this technology. In such circumstances, new guidelines are necessary to balance the risks and benefits of this new technology in specific disease conditions. In addition, it is crucial to understand the underlying mechanisms of ultrasonic functional biomaterials for precision drug therapy to optimize the treatment of diseases, and to overcome physical barriers for effective drug delivery.

From our point of view, the most important prospects, and problems of ultrasonic functional biomaterials for drug precision therapy are summarized as follows:

(**1**). Biosafety is an important reference index for clinical treatment. Therefore, new nano-carrier technologies need to be developed to overcome the challenges of biocompatibility. Coating or protective shell structures can be used to reduce the toxicity of ultrasonic response materials, control clearance rate and circulation time, to provide effective and safe treatment methods for diseases, which will be an important research direction of the precision treatment of ultrasonic biomaterials.

(**2**). Different organs and tissues have significant differences in the transmission of ultrasound. Therefore, it is necessary to design the best ultrasound mode for different target organs to improve the efficiency of ultrasound-triggering drug delivery. However, ultrasound systems used in most studies are not ideal for the overall effect of the organ. Therefore, the development of a new three-dimensional ultrasound system can be more systematically applied to organs, thus achieving a more uniform transmission of sound waves and higher efficiency of drug delivery to each target organ. It will be a great prospect for the precision therapy of ultrasonic functional biomaterials.

(**3**). Avoiding unnecessary biological thermal effects during treatment. In drug delivery, it is generally desired that the temperature within the target tissue is uniform and that the temperature be monitored and maintained within a certain range. Ultrasonic functional biomaterial systems should maintain constant tissue circulation temperature and remain responsive to ultrasound to control drug release at target sites. given that, the delivery system should be carefully designed to control a reasonable mechanical index range and make it have a specific temperature range, combined with an accurate monitoring system to optimize the precision drug treatment of ultrasonic functional biomaterials.

(**4**). One of the ultimate goals of tissue engineering is clinical transformation. Therefore, the design of intelligent ultrasonic functional biomaterials should strive to conform to FDA-approved formulations. At this point, research should focus on the technologies needed to trigger drug release and the way that they can be applied for approval. Then, ultrasound stimulation is highly consistent with the clinical setting and has long been used successfully. Accordingly, the clinical transformation of ultrasonic functional biomaterials is a hot direction that is expected to make a lot of breakthroughs in the future.

Conclusion:

The ultrasound technique and functional biomaterial precision drug therapy system is an exciting and unique therapeutic approach that can track drug delivery, control drug delivery in dose, space, and/or time, and improve drug deposition with high spatial precision, a large number of studies have shown that the drug precision therapy triggered by ultrasound combined with biomaterials has broad applications and therapeutic prospects. ultrasound provides a convenient and robust technology for drug triggering and precision therapy and is increasingly being studied and applied, the ultrasound system mainly triggers and realizes precise drug treatment through sonophoresis and sonoopermeation (including inorganic-based nanoparticles, microbubbles, nanobubbles, liposomes, micelles, micro-nanomotors, etc.).

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