The bright side of sound: perspectives on the biomedical application of sonoluminescence

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Light is a physical phenomenon that is very important to human life, and has been investigated in its nature, behaviour and properties throughout human history although the most impressive improvements in the use of light in human activities, and of course in medicine, began just two centuries ago. However, despite the enormous progress in diagnosis, therapy and surgery to assess health and treat diseases, the delivery of light sources *in vivo* remains a challenge. In this regard, several strategies have been developed to overcome this drawback, the most interesting of which is the involvement of ultrasound. In this review, the authors examine how ultrasound may improve light delivery *in vivo* with a special emphasis on one of the most intriguing ultrasound-mediated phenomena called sonoluminescence, which is the conversion of mechanical ultrasound energy into light.

Introduction

Light is linked in a wide variety of ways with biological phenomena such as vision, biological clocks and photosynthesis. These phenomena are so important that, without light, our world would be different, probably without life or at least inhospitable for all higher organisms that are around today. Due to the huge impact of light in human evolution, humans have tried, for centuries, to find out all the secrets about this phenomenon and how to take advantage from it. Due to this effort, nowadays, light influences the way we live in ways we could never have imagined just a few decades ago, in the ways we communicate, in the tools we use to explore the frontiers of science and, of course, in the practice of medicine. In this regard, in the 19th century the use of light was introduced in medicine, leading to a rapid increase in the knowledge of its physical nature and basic interactions with matter.

Currently, light and its related optical methodologies have achieved an extensive impact on current medicine, with various laser and optical instruments used in the clinical

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setting for diagnosis and therapy to evaluate health and cure diseases. Recent improvements, thanks to innovative medical lasers and new optical technologies, have revealed opportunities for further progress in photomedicine.[1–3] However, for all photomedicine approaches, the delivery of light sources *in vivo* remains a challenge. Recently, to overcome this significant drawback, a new idea has been suggested, mainly in the field of photodynamic therapy (PDT) and optogenetics, where ultrasound (US) seems to play an interesting role in triggering common photosensitizers[4] and in controlling cellular activity.[5] In this review, the authors discuss how US can improve specific areas of photomedicine, with a special emphasis on one of the most intriguing US-mediated phenomena called sonoluminescence (SL).

Application of light in medicine

In medicine, the use of light originates from its evolutionary function in biology, indeed the therapeutic use of light takes advantage of the biological effects on tissues derived from the specific wavelength absorption of a diversity of light-responsive molecules. In the human body, these light-sensitive molecules can be endogenous or exogenous, therefore, administered as drugs or inserted by gene-editing methodologies. To date, the main light applications can be subdivided into three main groups: (i) optical imaging, (ii) light-activated therapy and (iii) laser surgery.[3]

Optical methodologies are extensively utilized in diagnostic medicine, ranging from laboratory measurement and diagnostic imaging, to intra-surgery imaging and therapy monitoring. Thanks to the high spatial resolutions of light, optical imaging allows real-time visualization of cells and tissues by reasonably inexpensive and portable devices. Many different technologies for macro- and microscopic imaging have been implemented as a standard of clinical practice, and many others are under development for translation in the clinical setting. Surgical techniques such as laparoscopic surgery, which are based on optical guidance, have decreased the haemorrhage risk and lowered the time of patient recovery. Increased surgical results have also been achieved by using intra-surgery optical imaging with tissue contrast that can exceed what the human eye can distinguish.[3]

In 1960, T. Maiman provided the first evidence of the ruby laser application, paving the way to the great history of laser medical uses.[6] Pioneering studies employed photocoagulation for treating retina diseases, skin injuries and cardiovascular lesions. Nowadays, medical lasers are used in routine practice, as well as in ophthalmic surgery, dermatological treatment and tissue removal in internal body organs by using fibre-optics.[7]

One of the most intriguing properties of light is its capability of influencing photo-responsive cells, proteins and molecules that can be effectively exploited in therapeutic applications. Light-mediated treatments, namely phototherapies, rely on the use of an appropriate light source. These treatments, such as PDT, can be very useful for diseases in which unhealthy cells can be destroyed by light-induced oxidative stress. PDT is a clinically proven approach exerted in a variety of fields such as oncology, ophthalmology, dermatology and dentistry.[8] Recent innovations in nanomedicine have enabled the development of multimodal nanocarriers with numerous light-activated functions, including conversion of near infrared to visible light, photodynamic and photothermal therapies, drug delivery and imaging.[9]

Optogenetics represents a new frontier in light-activated therapies, enabling unprecedented control over neural activity and cellular signalling.[10] Indeed, optogenetic methodologies have opened up novel avenues into disease connections, leading to immediate clinical results. For instance, in mouse models, the optical section of brain connections has disclosed mechanisms for brain stimulation useful for treatment of Parkinson's disease.[11] Thanks to its neuromodulation capabilities, optogenetics has attracted interest for treating chronic pain,[12] depression[13] and laryngeal paralysis.[14]

However, to effectively exert the various biological effects induced by light–tissue interactions for clinical applications, light must be carried to the desired tissues with specificity and proper energy, therefore the development of new lasers delivering desired output characteristics will expand both clinical and at-home settings, as well as the development of new optoelectronic devices such as polymer LEDs.[3] Unfortunately, all these strategies still suffer from one of the main drawbacks about light delivery, namely the poor penetration of light due to intrinsic absorption and scattering within tissues. In this regard, several attempts have been made to overcome this drawback, with the most promising methods involving implantable optoelectronic devices.[15] Innovative instrument concepts and design involve implantable light emitting diodes,[16] drug delivery controlled by optofluidics[17] and optogenetic applications through miniaturized wireless optoelectronic instruments.[18,19] A new approach involves working with biomaterial photonic devices.[20] Biomaterial-based optical waveguides can be exploited for long-lasting delivery of light, and are required to be displaced if produced with biodegradable materials, such as absorbable sutures made of polyglycolic acid or silk.[21] Finally, taking advantage of the intrinsic properties of intracellular lasers to act on specific sites such as inflamed tissues, developing cell-based lasers can represent an innovative way to bring light with selectivity and the possibility to perform – at the same time – a strong multiplex imaging set on narrowband coherent emission.[22] Recently some researchers have suggested US as a new tool to overcome certain drawbacks and improve the light delivery, mainly in the field of PDT and optogenetics.[5,23–27]

Light from sound

Sound is a wave that transports mechanical energy through the local vibration of particles in an elastic medium with no net transport of the particles.[28] This definition is, of course,

very different from the definition of light because light is described as an electromagnetic wave with the same theoretical principles that govern all forms of electromagnetic radiation. Nevertheless, despite great differences between these two waves such as mechanical *versus* electromagnetic, a well-known phenomenon called mechanoluminescence (ML, Fig. 1) is able to transform mechanical energy, as well as mincing, smashing, distorting, splitting, shrinking or using US pulses, into light.[29] Thus, ML can have various applications such as magnetic and electric field detection, light source, dynamic pressure outlining or stress sensing.[30] Terasaki *et al.* showed the exploitability of ML as a light source following *in vivo* exposure to US radiation or for photocatalysis.[31,32] Terasaki and colleagues synthesized an ML nanoparticle with a size of 10 nm, small enough to be used as an ubiquitous light source in tissues and cells.[31] For this purpose, they investigated the ML induced by ultrasonic waves, detecting ML that depends on US irradiated power, then introducing the ultrasonic wave as a suitable candidate for mechanical stimulation to achieve ML.[32] However, these are just preliminary results to demonstrate the ability of US-induced ML as a light source, and many issues should be addressed before ML can be utilised as a ubiquitous light source in tissues, for example, the toxicity of the materials in living organisms.

ML is not the only mechanism through which mechanical energy can be transformed into light, in nature, a light emission by marine living organisms is very usual, triggered by the mechanical stimulation from water agitation that elicits cell deformations able to initiate action potentials into vacuole membranes, called bioluminescence (BL). The BL molecular mechanism is based on a classic two-component process composed of the luciferase enzyme catalysing the BL reaction, and the luciferin molecule acting as a light-releasing system during the reaction (Fig. 1).[33] Kheirolomoom and colleagues encapsulated D-luciferin, in long-circulating liposomes, showing that, after tumour exposure to US in Met1-luc tumour-bearing mice, an immediate emission of light was detected, enhancing *in vivo* bioluminescence imaging.[34]

Another mechanism for light emission is through a chemical reaction, which is called chemiluminescence (CL, Fig. 1).[35] In general, in direct CL, two essential mechanisms are responsible for the chemiluminescent reaction, commonly a substrate and an oxidant reagent, along with cofactors and often a catalyst, which react, generating a product or intermediate. In addition, a fraction of the product or intermediate will be generated in an electronically excited state, being able to emit photons after releasing to its ground state. On the other hand, in indirect CL, an energy transfer process from an excited molecule to a fluorophore is pivotal, which, once activated, is able to emit photons when relaxing to its ground state. This mechanism is relevant for molecules that cannot be engaged in direct CL reactions but that are able to transfer their excess energy to a fluorophore.[36] The referred reactions can be exploited in a great diversity of practical uses of CL, and recently Le *et al.* have investigated the combination of CL and US for dual imaging.[37] In this investigation, the relevant improvement of using CL with US has been demonstrated by using tissue mimicking materials and *ex vivo* models.[38,39] McMurray and colleagues suggested that the sonochemiluminescence intensity could be related to the concentration of $HO^{\bullet}$.[40] Recently, this mechanism has been confirmed by the fact that US irradiation of water can lead to acoustic cavitation, a process capable of generating free radicals such as $H^{\bullet}$ and $HO^{\bullet}$, which are able to produce reactive oxygen species (ROS) therefore, increasing CL.[41]

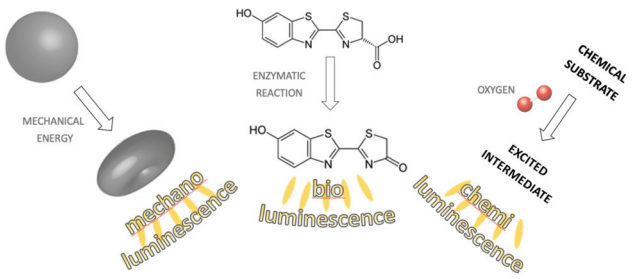

Fig. 1 Schematic illustration of the most known phenomena responsible for physical or chemical-mediated light emission.

Sonoluminescence

Acoustic cavitation, which is the mechanism that underlies sonochemiluminescence, refers to the mechanical interplay between acoustic waves and gas-filled microbubbles present in the exposed liquid.[42] Acoustic cavitation can take place either as a stable or transient mode. During a significant number of acoustic cycles, in stable cavitation, microbubbles oscillate close to an equilibrium radius without collapsing. Conversely, in transient cavitation, microbubbles grow by rectified diffusion reaching a resonance size, and then collapse. A variety of physical effects can, therefore, be generated when cavitation microbubbles oscillate or collapse, such as shear forces, shock waves and micro-jets. Moreover, the collapse of gas-filled microbubbles during transient acoustic cavitation is nearly adiabatic and produces a temperature in the thousand-degree range in the microbubbles for a very short time period.[43] Extremely reactive radicals are then generated thanks to these exceptional temperature conditions. For instance, if the cavitation medium is water, $OH^{\bullet}$ and $H^{\bullet}$ radicals are produced by the water homolysis. This generation of radicals has been exploited to perform, for example, organic pollutant degradation and synthesis of polymers or nanomaterials.[44] Furthermore, acoustic cavitation has also been found to be valuable in medical diagnosis and therapy.[45,46] In this regard, in biomedicine, recently the acoustic cavitation use has greatly improved thanks to its unique theranostic features and feasibility. The cavitation energy derived from the microbubble generation, growth, and collapse, can produce reversible poration of cell membranes and vessel walls, namely sonoporation, which can be used for delivery to the target site of bioactive elements such as drugs, genes, peptides or proteins.[47,48]

However, when cavitation microbubbles oscillate and collapse in liquids, another intriguing physical phenomenon

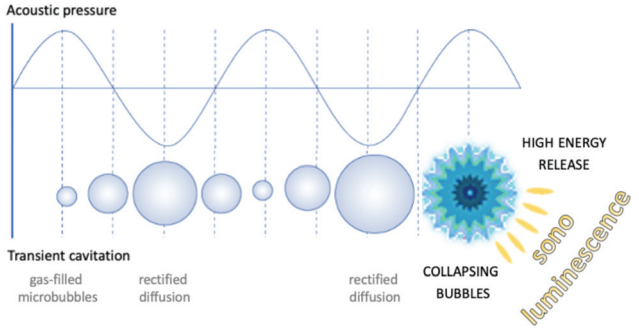

Fig. 2 Ultrasound-mediated SL relies on the occurrence of transient cavitation during US exposure of a liquid milieu leading to the formation of gas-filled collapsing microbubbles. Thanks to rectified diffusion, gas and vapour are transported into the microbubbles until they reach a critical size, and then they collapse. The microbubble contents are then compressed rapidly, resulting in extreme local conditions and a range of secondary effects that drive processes such as photon emission, dubbed SL.

occurs called sonoluminescence (Fig. 2), and nowadays it is well known that acoustic cavitation is also followed by light emission.[49] In simple terms, SL refers to the transformation of US mechanical energy into light pulses of about 35–350 picoseconds and composed of 3×10^4–3×10^5 photons.[50] This process is always inefficient, generally transforming only 0.0001 of acoustic energy into photons, however it is remarkable, as the occurring energy density of rising photons overcomes the US driving energy by a 10^{12} fold.[51]

In 1934, SL was accidentally observed at the University of Cologne by H. Frenzel and H. Schultes studying acoustic radar. The two scientists noticed that many of the microbubbles were flashing in the water. Created by highly powerful US fields, the flashing lights were chaotic and unpredictable. Later, this phenomenon was defined as multi-bubble sonoluminescence. After 50 years, F. Gatian and L. A. Crum began researching SL and were able to achieve single-bubble sonoluminescence (SBSL) for the first time. Effectively trapping a single microbubble in a flask, Gatian and Crum energized the microbubble, creating the first recorded SBSL.[52]

The discovery of SBSL initiated a powerful research activity mainly by physicists and obtained consideration from the broader scientific community just after it was suggested as a result of quantum radiation or when it was proposed to be able to produce nuclear fusion. Noteworthy, the representation of SL as a "hot spot", namely the thermal model, is the universally accepted one, and the model related to the generation of nuclear fusion has been widely rejected.[52] Therefore, the main question is: could SL have a potential for applications in the biomedical field?.

The first evidence of a biomedical application of SL comes from a Russian study where the authors proposed detecting SL in blood plasma in the differential diagnosis of tuberculosis, cancer and sarcoidosis of the lungs.[53] Unfortunately, the manuscript was written in Russian therefore not easily communicating the real achievements to the wider scientific community. In 1996, other Russian scientists published a short manuscript in English, in which 8000 patients with cancer, tuberculosis and some other diseases were enrolled to investigate the possible applications of SL in diagnostics. The results show that the SL-method is a promising technique for early diagnostics of cancer, tuberculosis and low-immunity status. Due to the small samples of blood required and the speed of the analysis, this approach could be prospective for mass people examination.[54] Recently, A. Casacchia and colleagues developed an experimental apparatus for producing SBSL and subsequent measurement of radial oscillations using optical scattering techniques, allowing the effective characterization of both the biological fluid content and viscoelasticity on the spectra of SBSL light emissions, opening new perspectives of SL in diagnostics.[55]

Photodynamic therapy

Suggesting a possible practical application of SL in the biomedical field, we can pose the question "in which therapeutic applications could SL be feasible", and PDT is the most likely answer. PDT makes use of harmless chemical compounds (photosensitizers) such as porphyrins, chlorophylls, and other dyes that are employed to cause precise bioeffects on cancer cells following light irradiation. However, this technique may have limited effectiveness in thicker tumours since it possesses a poor penetration depth.[56] Therefore, to overcome this drawback, a strategy to activate the photosensitizer in deeper tissues is to deliver laser light to the target site through fibre-optics. Thus, nowadays laparoscopic intraoperative incisions and endoscopic procedures are needed to reach the target area and activate the photosensitizer by laser.

The photosensitizer absorption of a proper energy photon causes the molecule to achieve a singlet state excitation. The photosensitizer can then go through intersystem crossing to a triplet state of lower energy. On the assumption that the triplet state has an increased sufficient energy, its decay back to the ground state may have two effects. Firstly, a type I reaction takes place by transfer of an electron to molecular oxygen, leading to the formation of a superoxide radical, thereby initiating a cascade of radical reactions, which damage biomacromolecules and kill cells in the close proximity. A reaction of type II takes place through transfer of energy to oxygen, which is promoted from a ground triplet state to a cytotoxic excited singlet state. Singlet oxygen and radicals cumulatively defined as ROS can cause apoptotic and necrotic cell death.[57]

Almost all of the porphyrin-derived photosensitizers are excited in the blue region of the visible spectrum, and SL emission is also intense in the same region of the electromagnetic spectrum, raising the question whether SL is able to produce a photon amount sufficient to excite porphyrin-derived photosensitizers. Since US is able to reach deep tissues in living organisms, the answer to this question may help to overcome the main drawback in PDT, since the in-depth delivery of PDT relies on relatively invasive approaches.

The first experiments about the possibility of SL employed as an inner source of light to activate other molecules in solu-

tion were performed by M. Ashokkumar and F. Grieser in 1998.[58] These authors investigated the excitation of pyranine in water by SL and the ensuing emission, which can be referred to as sonophotoluminescence, drawing the conclusions that photosensitizing chemical compounds inside the human body can be excited *via* sonophotoluminescence produced through US as an outer source with respect to the human body. The same authors also investigated other different sensitizers, namely fluorescein, eosin and pyrene where SL, produced in air-saturated non-aqueous and aqueous solutions, was able to directly excite these species, leading to fluorescence emission.[59] Recently, Beguin and colleagues have published a work where therapeutic US was able to produce SL when phospholipid-coated microbubbles were added in aqueous solution. This investigation provides a mechanistic explanation about the anticancer approach, called sonodynamic therapy (SDT), where light-responsive chemical compounds were able to be excited through US-mediated cavitation.[60]

Sonodynamic therapy

The first evidence about SDT came from a study by Yumita *et al.* in 1989, where various hematoporphyrin derivatives employed in PDT also caused a relevant cell damage after being exposed to US.[61] Since then, it has been shown that SDT can treat solid tumours,[62–65] leukaemia[66] and atherosclerosis[67] and, moreover, remove proliferative scars and kill pathogenic microorganisms.[68,69]

Since SDT was developed on the basis of PDT, some suggest that SDT shares a similar therapeutic mechanism where the ultrasonic wave triggers the sonosensitizer inside the target tissue, with production of ROS that kill the target cells.[70] Even though there is consensus in ROS production as the main cell killing mechanism, less is known about the mechanism underlying ROS production. At present, two hypotheses have been suggested to explain the mechanism of ROS production following exposure of the sonosensitizer to US wave energy, namely the pyrolysis hypothesis and the SL hypothesis (Fig. 3).

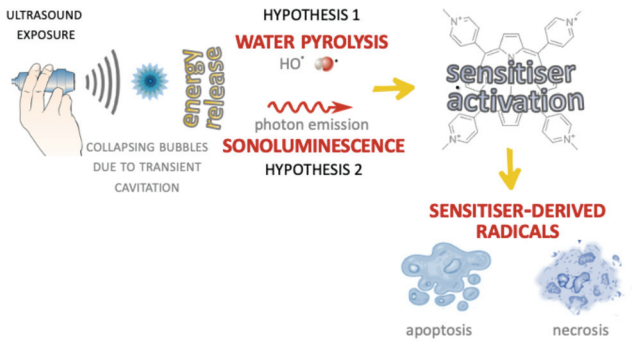

Fig. 3 Schematic illustration of the two main hypotheses concerning the underpinning mechanism of sonodynamic activity. The sensitizer activation leading to radical-mediated cell death can be driven by water pyrolysis or SL induced by the energy release of the collapsing microbubbles.

Both hypotheses are based on the acoustic cavitation phenomenon; according to the first hypothesis, sonosensitisation arises from the sonosensitizer activation nearby or inside the hot collapsing cavitation microbubbles leading to formation of sensitizer-derived radicals *via* direct pyrolysis or indirect reactions with HO$^{\bullet}$ and H$^{\bullet}$ radicals derived from water pyrolysis. These are mainly carbon-centred radicals and are also able to interact with oxygen-generating alkoxyl and peroxyl radicals. In contrast to H$^{\bullet}$ and HO$^{\bullet}$ radicals, also generated by pyrolysis in the cavitation microbubbles, the alkoxyl and peroxyl radical reactivity with organic components is lower, and they therefore have an increased probability of reaching pivotal cellular sites killing target cells. This hypothesis is the most supported by researchers involved in this field even though some evidence has revealed, as mentioned before, that SL seems to play a role, as also suggested from the studies by Giuntini *et al.* and Dezhkunov *et al.*[24–71] In particular, Giuntini and colleagues pointed out how the activation of a metal-porphyrin complex by US exposure, namely sonodynamic activation, is more likely due to SL-induced photoactivation rather than to pyrolysis, the radical generation occurring through the homolytic bond rupture of water molecules.

Conclusions

In this review we have discussed the possibility of overcoming the poor penetration of light in tissues and the invasiveness of diverse optical strategies, changing the sound into light to improve, mainly, the photodynamic and optogenetics approaches *in vivo*. We have therefore discussed about SL and how this intriguing phenomenon deserves more attention. However, every kind of new advancement and achievement, mainly in the scientific field, has its own limitations which make rigorous challenges. In this regard acoustic cavitation, considered one of the primary mechanisms underpinning STD and SL, represents the most important challenge in this field. Therefore, additional mechanistic studies have to be conducted to develop efficient methods to easily handle acoustic cavitation with the final aim to directly measure and monitor its effects. These improvements in acoustic cavitation comprehension will also open new perspectives about the SL, evolving this phenomenon, from a physics laboratory curiosity to a reliable, convincing and solid technique to deliver light for *in vivo* applications.

Conflicts of interest

There are no conflicts to declare.

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