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Enhanced sonochemical reaction by phase-change nanodroplet
相変化ナノ液滴による音響化学作用の促進効果

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1. Introduction

In ultrasound echography, microbubbles are the most commonly used contrast agent. They show high echogenicity and characteristic non-linear acoustic responses, which enables their acoustic echo signals distinguishable from other signals by using appropriate ultrasound exposure sequences and filters.

Recently, it has been revealed that microbubbles have possibilities to be used as sensitizers for HIFU therapy because they have been found to enhance temperature rise induced by tissue absorption of ultrasound energies. [1-3].
However, a serious problem in utilizing microbubbles is that their sizes (several microns in diameter) are too big to leak into tissues from blood vessels when administered intravenously.

To solve the problem, we are developing a nano-sized ultrasound contrast agent which turns into microbubbles upon the exposure of ultrasound pulses. We reffer it as phase change nano droplet (PCND).

We aim to administer PCND and change them into microbubble only at the target inside body. In such a way, we could visualize if the droplets are accumulated at the target tissues. Then we could further expose therapeutic ultrasound such as HIFU for site-specific treatment. Because it is an on-demand generation of microbubbles and not requires an incubation time for bubble acumulation at the target, almost all bubbles generated are usable for therapeutic purposes.

In our previous work, we investigated the effect of PCND on accelerating inducing cavitation not temperature rise induced by using 1-MHz ultrasound for developiong synergestic cavitational and thermal therapy of tumors.

In this study, we preformed preliminary experiments on the chemical activities of PCND-inducd cavitation to investigate if tumor therapy with multidisciplinary tumor treatment with thermal, mechanical, and chemical effect would be possible by using PCND.

2. Materials and Methods

PCND preparation

The preparation procedure of PCND was described elsewhere [4]. Briefly, DPPC liposome was prepared and the liposome was further emulsified at high pressure (20 MPa) in the presence of perfluorocarbon liquids. The size distribution of PCND was measured with a LB-550 (Horiba, Ltd., Kyoto, Japan) dynamic light-scattering size analyzer. The mean diameter of the PCND was about 0.3 μm.

Experimental setup for ultrasound exposure

Focused ultrasound transducer (2.2 MHz with a diameter of 35 mm or 1.1 MHz with a diameter of 48 mm) were submerged in water tank filled with degassed water kept at 37 ºC. Specimen was placed at the focus of the transducer. Ultrasound was exposed for 20 s.

Iodide oxidation

For a quantitative measurement of chemical activity of PCND-induced cavitation, a typical reaction induced by hydroxyl radicals was used. The reactant consists of 0.1 M potassium iodide and 0.1 M chloral hydrate, the latter for a catalytic agent of oxidation. Ultrasound exposure was performed for 15 s to a 2-ml aliquot of reactant in a 0.03-mm-thick polyethylene bag with an inner diameter of 10 mm. The concentration of the reaction product, tri-iodide ion, was determined spectrometrically by measuring the optical density at 350 nm of the reactant.

3. Results and Discussion

We measured chemical reaction rate induced by the cavitation induced in the presence of PCND, utilizing the oxidation of iodide to tri-iodide as a measure. The reaction is believed to be induced by hydroxyl radicals which is known to have potentials to be involved in obtaining chemical anti-tumor effects.

Up to 800 W/cm^2, the maximum acoustic intensity used in this series of experiments, no significant oxidation was observed without the addition of PCND, possibly because we used an acoustically almost transparent reaction vessel thus no significant standing wave field could be expected. It is very natural not to observe the chemical reaction even at acoustic intensities as high as 1 kW/cm^2 without the aid of standing wave fields.

In Fig. 1, the chemical reaction rate obtained in the presence of PCND is shown as functions of acoustic intensity. In this experiment, ultrasound pulse at acoustic intensity of 1.2 kW/cm^2 with a cycle number of 50 was used as the triggering ultrasound for inducing microbubbles from PCND.

The presence of the triggering ultrasound significantly lowered acoustic intensities required for inducing the chemical reaction. In the figure, the threshold for inducing chemical reaction was about 0.6 kW/cm^2 without trigger and those with triggering ultrasound was less than 0.3 kW/cm^2. The result suggests that PCND works efficiently as a cavitation nucleus not directly but as the form of microbubble. In the figure, it is shown that the frequency of triggering ultrasound is an important factor for the oxidation rate. The tendency was that The higher the frequency, the higher the reaction rate.

Because the triggering ultrasound has a very short duration, the presence of the triggering ultrasound does not increase the temporally averaged ultrasound intensity significantly. Even at 1 kHz, the highest frequency in the figure, the averaged intensity is less than 1.2 times of that without triggering ultrasound. The obtained result is not thus considered to be relevant to the temporally averaged acoustic intensity. Fig. 2 shows the details on the influence of the averaged intensity. The figure shows the same results as in Fig. 1 by changing the horizontal axis to averaged acoustic intensity. No significant difference from Fig. 1 is observed. A plausible explanation for the effect of frequency of the trigger is that hydroxyl radical species are very short lived and easily quenched by surrounding chemical species such as water molecules. In such a case, successive induction of hydroxyl radical is needed for yielding chemical reaction because no other cavitation nuclei than PCND exist in the system. PCND-induced microbubbles are transient and may work for only less than 10 ms.

Results obtained this time give information on bubble generation and following cavitational effects with PCND. To effectively induce microbubbles, the frequency of triggering ultrasound should be more than 100 Hz. Such number may be related to the composition of perfluorocarbon species incorporated in PCND. In this experiment, a mixture of perfluoropentane and perfluorohexane were used. The former tends to produce stable microbubbles and the other produce rather transient ones.

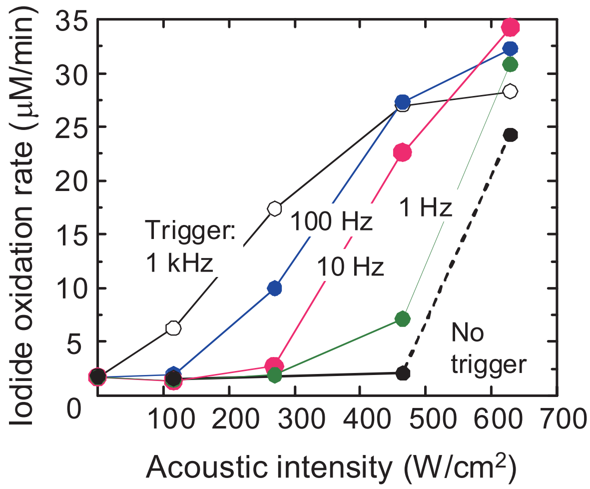

Fig. 1 Chemical activity of PCND-initialized cavitation as functions of acoustic intensity
(Freq.: 1.1 MHz, triggering pulse: 1.2 kW/cm^2, 50 cycles, PCND conc. : 4 mg/ml)

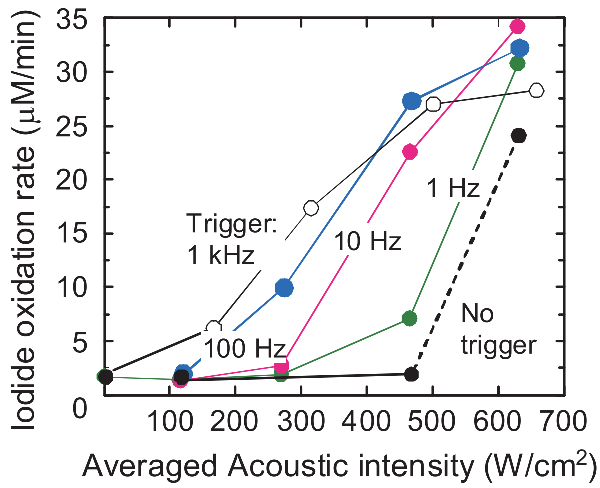

Fig. 2 Chemical activity of PCND-initialized cavitation as functions of temporally averaged acoustic intensity (same data as Fig. 1)

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