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Review

Measurement of Specific Loss Power from Intracellular Magnetic Nanoparticles for Hyperthermia

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Abstract

Magnetic nanoparticles have been studied extensively for biomedical applications over the past decades. One of the promising applications of magnetic nanoparticles is hyperthermia which is heat treatment for cancer. For hyperthermia application, it is essential to develop magnetic nanoparticles with high heating efficiency and optimize the condition of magnetic field to achieve adequate heat at tumor. Here, we discuss the heating mechanism of magnetic nanoparticles, influence of intracellular environment for magnetic behavior and heat dissipation, and recent advance on heating evaluation.

Keywords: Magnetic nanoparticles; Magnetic hyperthermia; Relaxation losses

Introduction

Nanomedicine which uses nanotechnology for diagnosis, prevention, and treatment has been growing rapidly for the last few decades. Various nanomaterials have been developed for the field of nanomedicine such as liposomes [1,2], polymeric nanoparticles [3], Micelles [4], dendrimers [5], magnetic nanoparticles [6,7], and gold nanoparticles [8]. Among those nanoparticles, magnetic nanoparticles have been attracting attention due to their unique magnetic properties. Large microscopic field gradients induced by magnetic nanoparticles under magnetic field causes shortening of longitudinal relaxation time (T_1) and transverse relaxation time (T_2) of water proton [9]. This property makes magnetic nanoparticles strong contrast agents for magnetic resonance imaging (MRI) [10,11]. Some of the contrast agents using iron oxide nanoparticles (Fe_3O_4 or γ-Fe_2O_3), which are the most commonly used magnetic nanoparticles for biomedical applications, have been approved for clinical use [12]. Magnetic guidance ability of magnetic nanoparticles can be used for drug delivery [13,14] and gene transfection [15]. Drug delivery to specific targeted site reduces side effect from non-specific distribution. Moreover, magnetic nanoparticles can be used as heat source for hyperthermia (heat treatment) due to heat generation under AC magnetic field [16,17]. Capability for both of diagnosis and treatment makes magnetic nanoparticles promising material for nanomedicine.

Hyperthermia

It has been well known that temperature rise in the range of 40–47°C kills cells in a time and temperature dependent manner [18]. Hyperthermia is heat treatment of cancer based on this temperature sensitivity of cells. In addition to the heat sensitivity, hypoxic cells (poorly oxygenated cells) in tumor shows higher sensitivity to heat compared to cells in healthy tissue [19]. If the temperature is well controlled at tumor site, hyperthermia would cure cancer without causing damage to surrounding healthy tissues. These concepts make hyperthermia attractive compared to the traditional cancer treatment which cause side effect. Combined treatment of hyperthermia and traditional cancer treatment such as chemotherapy and radiotherapy has been reported to increase treatment effect [19].

Various heating methods have been developed such as water bath for whole body hyperthermia, and using microwave, radio frequency, and ultrasound as external energy sources for regional hyperthermia treatment [20]. However, regional hyperthermia using external heat source has limitation on penetration which prevent treatment for deep-seated tumors, and unavoidable heating of healthy tissue between heat source and tumor is the drawback. Magnetic nanoparticles have been a great candidate as a heat source for local hyperthermia treatment due to their ability for magnetic targeting and heat induction under AC magnetic field at specific region. Hyperthermia using magnetic materials was first proposed in 1957, Gilchrist et al. reported heating of various tissue samples with γ-Fe_2O_3 under AC magnetic field [21]. Since then, hyperthermia using magnetic nanoparticles (called magnetic hyperthermia or magnetic fluid hyperthermia) has been investigated extensively including heating mechanism [22], heating efficiency [23], and *in vitro* and *in vivo* study [24,25]. Furthermore, clinical trials of magnetic hyperthermia have been conducted in Germany [26].

Heating Mechanism of Magnetic Hyperthermia

Heat dissipation of magnetic nanoparticles under AC magnetic field is caused by two processes, hysteresis loss and relaxation

losses. When an external magnetic field is applied, magnetic materials possess hysteresis property between magnetic field and magnetization. Hysteresis loss is induced by this hysteresis property, and its value is given by its frequency multiplied by the area of the hysteresis loop in an external field [27]. For small magnetic nanoparticles, relaxation losses are dominant for heat dissipation of the nanoparticles. Relaxation losses are caused by a delay in magnetic moment relaxation. Brownian relaxation loss and Néel relaxation loss are associated with magnetic moment rotation of the entire particle and within a particle, respectively [28]. The Brownian relaxation time τ_B and Néel relaxation time τ_N are given by the following *equations*:

$$\tau_{\mathrm{B}} = \frac{3\eta V_{\mathrm{H}}}{k_{\mathrm{B}}T} \quad (1)$$

$$\tau_{\mathrm{N}} = \tau_0 \exp\left(\frac{KVm}{k_{\mathrm{B}}T}\right) \quad (2)$$

where η is the viscosity of the suspended fluid, V_H is the hydrodynamic volume of magnetic nanoparticles, k_B is the Boltzmann constant 1.38×10^{-23} J/K, T is the temperature in Kelvin, τ_0 is the attempt time of $\sim10^{-9}$ s, K is the magnetocrystalline anisotropy constant, and VM is the volume of the magnetic core. Brownian and Néel relaxations occur in parallel. Thus, effective relaxation time is described as

$$\frac{1}{\tau} = \frac{1}{\tau_{\mathrm{B}}} + \frac{1}{\tau_{\mathrm{N}}} \quad (3)$$

The heat dissipation by relaxation loss is given by the following equation [28]:

$$P_{\mathrm{relax}} = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2} \quad (4)$$

where μ_0 is the permeability of free space, χ_0 is the initial susceptibility, H is the amplitude of the magnetic field, f is the frequency of the magnetic field, and τ is the relaxation time. As shown in equation (1) and (2), Brownian and Néel relaxation times are dependent on viscosity of surrounding environment, hydrodynamic size and core size of magnetic nanoparticles, and their magnetocrystalline anisotropy.

Heating efficiency of magnetic nanoparticles is evaluated by calculating the specific loss power (SLP) or Intrinsic loss power (ILP). SLP provides power dissipation per unit mass of magnetic nanoparticles. Since SLP varies with the amplitude and frequency of applying magnetic field, ILP is introduced to evaluate heating efficiency of magnetic nanoparticles system-independently [29]. SLP and ILP are calculated as

$$\mathrm{SLP} = c\frac{m_{\mathrm{sample}}}{m_{MNPs}}\frac{\mathrm{d}T}{\mathrm{d}t} \quad (5)$$

$$\mathrm{ILP} = \frac{\mathrm{SLP}}{H^2 f} \quad (6)$$

where c is the heat capacity of water, msample is the mass of the sample, m_{MNPs} is the mass of the magnetic nanoparticles in the sample, and dT/dt is the slope of the temperature rise [30][29].

Although SLP and ILP have been used to evaluate heating efficiency of magnetic nanoparticles, inaccuracy of temperature measurement and lack of consistent measurement system prevent accurate evaluation. As discussed in Wildeboer's report, there is a need for a standardized measurement method for magnetic hyperthermia [31]. In addition to the measurement system, the condition of samples such as volume and shape is limited for the temperature measurement under magnetic field with high amplitude and frequency, and the temperature range is also limited from room temperature to below 100 ℃. There is a report showing that initial temperature slope which is used to calculate SLP varied with many factors such as sample volume and temperature sensor position [32].

To overcome these limitations, we proposed a novel way to evaluate heat dissipation of magnetic nanoparticles using AC hysteresis measurement. This measurement gives us dynamic magnetization curve which includes both of hysteresis loss and time lag of magnetization (relaxation losses) from magnetic nanoparticles. The heat dissipation can be directly calculated from the area of this dynamic magnetization curve called AC hysteresis loop. The correspondence between SLP calculated from AC hysteresis loop and temperature rise has been reported [33]. In addition to the reliability of measurement, this method shows magnetic behavior under AC magnetic field and can be used under wide range of amplitude and frequency.

Improvement of Heating Efficiency

The challenge lying in front of magnetic hyperthermia is delivery of magnetic nanoparticles and adequate heat generation under AC magnetic field which is safe for human body. Although delivery of magnetic nanoparticles can be improved using magnet, the magnetic guidance lacks site specificity. To achieve site specific targeting, localization of magnetic nanorods using pulsed magnetic field has been reported [34]. Ligand conjugation on the surface of nanoparticles can be introduced to enhance active targeting to the specific site which expresses receptor [1,35].

Due to the limitation on the quantity of magnetic nanoparticles and magnetic field, it is essential to develop magnetic nanoparticles with high heating efficiency. As shown in equations (1)-(4), heat dissipation from relaxation losses depends on the viscosity of surrounding environment, hydrodynamic size and core size of magnetic nanoparticles, and their magnetocrystalline anisotropy. Tuning magnetocrystalline anisotropy is one of the ways to improve heat dissipation of magnetic nanoparticles. Lee et al developed magnetic nanoparticles with optimal range of magnetocrystalline anisotropy using core–shell structure [36]. Since magnetocrystalline anisotropy is intrinsic material

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property, they introduced core-shell structure with $CoFe_2O_4$ in the core and $MnFe_2O_4$ in the shell to tune magnetocrystalline anisotropy by interfacial exchange interaction between hard and soft magnetic phases. Significant enhancement in heat dissipation has been reported for the core-shell nanoparticles compared to traditional magnetic nanoparticles.

It is known that magnetic behavior of magnetic nanoparticles changes with the surrounding environment [37]. As shown in equation (1), Brownian relaxation time depends on the viscosity of suspended fluid and hydrodynamic size of nanoparticles. It has been discussed repeatedly whether particles are free to move or immobilized in tumor tissue or inside cells after delivery to the target site or cellular internalization. Latter case limits heat generation from Brownian relaxation due to the inhibition of Brownian motion (Figure 1). Dutz et al reported static magnetic properties of magnetic nanoparticles injected into mice tumor [38]. Immobilization of magnetic nanoparticles in tumor was observed from the increase in coercivity and remanent magnetization of magnetic nanoparticles after injection into tumor. Similar tendency was observed for magnetic nanoparticles immobilized by gelatin compared to the nanoparticles suspended in fluid. Fortin et al reported temperature rise of magnetic nanoparticles which are internalized into human prostatic adenocarcinoma cells (PC3) [39]. The cellular internalized magnetic nanoparticles showed lower temperature rise compared to the same nanoparticles dispersed into water. Corato et al reported SLP of magnetic nanoparticles in water, on the cell membrane before internalization, and after internalization into human adenocarcinoma SKOV-3 cells [40]. Rapid fall in SLP value was observed after association of magnetic nanoparticles with the cell membrane and internalization.

AC hysteresis measurement is beneficial for understanding magnetic behavior of magnetic nanoparticles under AC magnetic field as well as estimating heat dissipation. We observed AC hysteresis loops of magnetic nanoparticles with the core diameter of 10 nm prepared in three different states; liquid sample which is dispersed in water, immobilized sample fixed with an epoxy bond, and cellular sample internalized into HeLa cells, and estimated specific loss power (SLP) [41]. Immobilized nanoparticles and cellular internalized nanoparticles showed lower SLP compared to liquid sample (Figure 2). This indicates that rotations of nanoparticles are inhibited inside the cells. Slightly lower SLP of cellular sample compared to immobilized sample suggests that rotations of magnetic moments are also inhibited by dipole-dipole interactions inside cells due to the partial agglomeration of magnetic nanoparticles [42]. We also estimated specific loss power (SLP) of magnetic nanoparticles in a single cell [41].

Magnetic properties of magnetic nanoparticles and the conditions to optimize their heating efficiency are well understood when they are magnetically independent [43]. However, previous reports suggest that both of blocking of Brownian motion from cell-particle interaction and magnetic interactions between each particle due to dense population of nanoparticles can affect to heat dissipation of magnetic nanoparticles inside cells [39-42]. Therefore, it is essential to understand the magnetic properties and heating mechanisms of magnetic nanoparticles within intracellular or intratumoral environment and under magnetic interactions to develop optimal magnetic nanoparticles for hyperthermia.

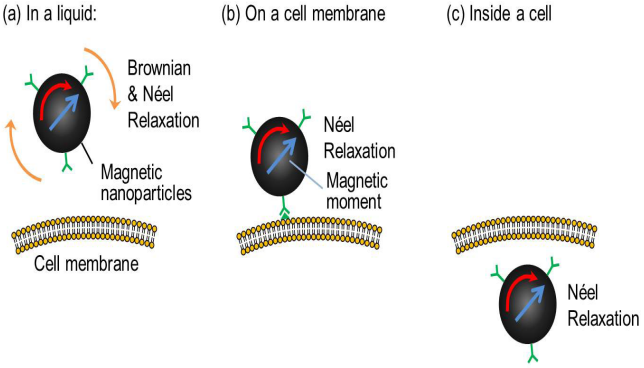

Figure 1. Schematic illustrations of magnetic nanoparticle behavior in a liquid (a), on a cell membrane (b), and inside a cell (c) under AC magnetic field. In a liquid, magnetic nanoparticles are expected to induce heat by both of Brownian and Néel relaxation losses. Only Néel relaxation loss is expected to contribute to heat dissipation for magnetic nanoparticles immobilized on a cell membrane or inside a cell.

Conclusion

There has been a significant improvement in theoretical study of magnetic relaxation and relaxation losses in the past few years [44,45]. However, inaccurate temperature measurement and lack of consistent measurement system make it difficult to give accurate value of SAR and ILP in experimental study [31]. As an alternative method, AC hysteresis loop measurement was suggested to evaluate SAR and ILP without measuring actual temperature rise. In addition, theoretical study of magnetic hyperthermia in cellular environment model has been

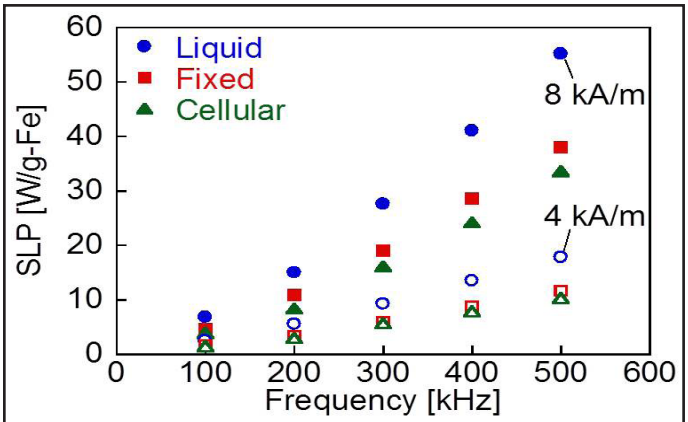

Figure 2. The frequency dependence of the specific loss power (SLP) estimated from the areas of AC hysteresis loops. Magnetic nanoparticles was prepared in liquid (circle), fixed with an epoxy bond (square), and internalized into HeLa cells (triangle). The amplitude of the magnetic field was 4 kA/m (open) or 8 kA/m (filled).

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reported [46]. Since heat dissipation of magnetic nanoparticles varies with surrounding environment, SAR evaluation needs to be done in models such as intracellular and intratumoral environment. We also demonstrated that relaxation losses of intracellular nanoparticles can be calculated using AC hysteresis measurement [41].

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