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Review article

Towards nanomedicines of the future: Remote magneto-mechanical actuation of nanomedicines by alternating magnetic fields☆

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ABSTRACT

The paper describes the concept of magneto-mechanical actuation of single-domain magnetic nanoparticles (MNPs) in super-low and low frequency alternating magnetic fields (AMFs) and its possible use for remote control of nanomedicines and drug delivery systems. The applications of this approach for remote actuation of drug release as well as effects on biomacromolecules, biomembranes, subcellular structures and cells are discussed in comparison to conventional strategies employing magnetic hyperthermia in a radio frequency (RF) AMF. Several quantitative models describing interaction of functionalized MNPs with single macromolecules, lipid membranes, and proteins (*e.g.* cell membrane receptors, ion channels) are presented. The optimal characteristics of the MNPs and an AMF for effective magneto-mechanical actuation of single molecule responses in biological and bio-inspired systems are discussed. Altogether, the described studies and phenomena offer opportunities for the development of novel therapeutics both alone and in combination with magnetic hyperthermia.

1. Introduction

The field of nanomedicine and drug delivery has undergone explosive development over the last decade. This development was prepared by the early work on the nanoparticulate drug carriers such as liposomes, drug–polymer conjugates, polymeric micelles, polyion complexes, and degradable nanoparticles in the 1980s and early 1990s. By the new millennium the nanomedicine and drug delivery field has become defined as a cross-section of medical, pharmaceutical, and biochemical engineering research that focuses on advanced therapeutic modalities of the base of nanomaterials ranging from about 10 nm to about 100 nm in diameter. The term "nanomedicine" that emerged in science fiction and art very rapidly became anything but fantasy as dozens of nanoscale size therapeutics received marketing approval and many more new ones have entered clinical evaluation [1–6].

From the standpoint of the drug delivery science the nanomedicine tasks include 1) efficient loading of the drugs or biomacromolecules into a nanoparticulate carrier, 2) safe delivery of the loaded carrier to the target organ and/or cell in the body, and 3) timely release of the payload. Selected nanomaterials are being themselves sought as therapeutic, diagnostic or theranostic modalities that in some cases need to be actuated at the site of the action. The first task — loading has been addressed very well, for what purpose scientists initially adopted nanoscale structures already discovered by polymer and material sciences and then followed up by invention of the whole range of new nanomaterials specifically tailored for the drug delivery purposes such as block ionomer complexes, PRINT (*P*article *R*eplication *I*n Non-wetting *T*emplate) nanoparticles and others. The second task remains a field of active research and discovery, where we have lately seen some successes and setbacks. Major challenges remain such as passive and active targeting, safety, host organism immune response, avoidance or employment of the reticuloendothelial system (RES), cell transport and endosomal escape. In spite of these challenges, however, we can reliably deliver therapeutically effective doses of some major anti-cancer and other medications using nanoformulations and have shown that these formulations can improve the therapeutic index compared to

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non-formulated molecules. The third task has not been addressed and is the field where the advances are still superficial at best. Poor drug release at the target site has hindered liposomal and micellar drugs and arguably is a major challenge for all DNA and protein delivery [7,8]. The nanomedicines of the future should provide for controlled release of the therapeutic agents, selective induction of cancer cell apoptosis, and other tasks that can be remotely actuated once these nanomedicines reach the site of their action [9–13]. Therefore, the search for the stimuli-responsive nanocarriers and versatile means for remote actuation of the cargo is an unmet need in nanomedicine. There have been many attempts to use chemical cues to trigger the target-specific release, such as acidic pH in the tumors, low endosomal/lysosomal pH, reductive intracellular environments, and tumor specific-enzymes (cathepsins, metalloproteases, etc.) [14–16]. However, one should admit that the fidelity and robustness of these strategies might not be sufficient to achieve the desired goals.

Alternative approaches employ physical fields such as ultrasonic and ionizing irradiation, photodynamic/photothermal treatment, or electromagnetic field that can remotely affect the nanocarriers and their environment in the body [17–22] (Fig. 1). Of these fields the electromagnetic field offers substantial benefits for nanomedicine and controlled drug delivery as a remote actuation tool. Much of the early efforts focused on the use of radio frequency (RF) magnetic field and magnetic nanoparticles (MNPs) in magnetic hyperthermia used to kill cancer cells of trigger release of the drugs from heat sensitive nanocarriers (liposomes, vesicles, dendrimers, nanogels) [23–30]. More-recently, however, the attention has begun shifting to the very distinct effects of a magnetic field exerted on MNPs, namely the magneto-mechanical phenomena, which can be observed in an alternating magnetic field (AMF) of much lower frequency and in the absence of heating [31–33]. This new direction offers in our view enormous opportunities to nanomedicine and the drug delivery field. However, its future success is critically dependent upon a deep and cross-disciplinary understanding of the biological, chemical and physical phenomena underlying the interactions of the MNPs with the electromagnetic field and surrounding polymer cell and tissue environments. In this review, we focus primarily on these interactions rather on the current and future strategies for the design of the nanomedicines incorporating MNPs. Such strategies could be very diverse and there is no doubt that the mature and resourceful nanomedicine community will employ their skills and ingenuity to exploit the existing opportunities to use these novel materials to improve human health. We hope that the present review will be of help to this community. To this end, we first discuss some general principles of the interaction of a magnetic field with biological systems. Then, we provide a brief overview of the use of MNPs in RF magnetic hyperthermia, followed by a thorough consideration of the magneto-mechanic effects that are outside and beyond the classic hyperthermia concepts. Finally, we describe some physical models both published in literature and some extensions that could be helpful in understanding the magneto-mechanic phenomena and effects of non-heating super-low and low frequency magnetic fields.

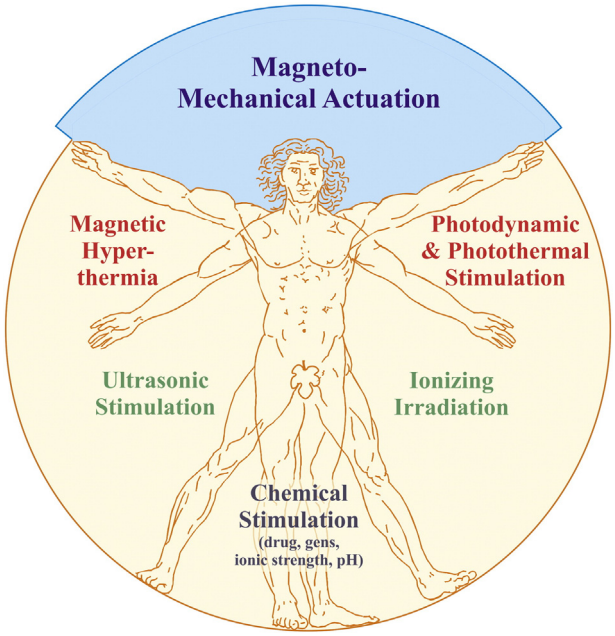

Fig. 1. Various strategies for remote actuation of nanomedicine and drug delivery systems.

2. Basis for the effects of magnetic field on biological processes

The thermal, electrochemical and electrophoretic effects of an electric/electromagnetic field have been well known and long used in therapy [34–36]. More recently the opportunities for the use of the magnetic field have attracted considerable attention. The AMF with a frequency f below 0.1 MHz is considered safe and can penetrate tissues (>1 m), which allows effective exposure of all potential targets in the human body [37].

Of course the direct effect of a magnetic field with conventionally used inductions ($B = 0.1$–1 T) on the chemical bonds is insignificant. Such field is considered "weak" from the thermodynamic point of view as the energy $U_M \approx \mu_B B$ that such field can transmit to one electron (ion, radical, atom) is negligible compared to the energy of activation of biochemical reactions $U_a \approx 0.1$–1 eV. In fact the U_M value is several orders of magnitude less than the thermal energy $U_T \approx k_B T_R \approx 0.026$ eV at room temperature T_R (here $\mu_B = 9.274 \cdot 10^{-24}$ A · m^2 — the Bohr magneton; $k_B = 1.38 \cdot 10^{-23}$ J/K — the Boltzmann constant). For example, for an electron, the paramagnetic center or radical $U_M \approx 10^{-3} U_T$ at $B = 0.5$ T и $T_R = 300$ K. The effects of the vortex electric field at the AMF frequency $f \ll 0.1$ MHz and amplitude $B < 1$ T on the ions and electrons are also negligible. The Coulomb and Lorentz forces in this case are orders of magnitude lower than the threshold values of activation of the most sensitive biochemical systems such as ion channels and receptors of cell membranes (1 to 10 pN as measured by single molecule force spectroscopy) [38].

Therefore, the balance between the needed input and required energy of activation would make impossible any effects of magnetic fields with frequency < 0.1 MHz and amplitude < 1 T on the chemical and biochemical systems in the state of thermodynamic equilibrium. However, the biochemical reactions and processes in cells and living organisms are not in thermodynamic equilibrium. As a result, the AMF and accompanying vortex electric field can affect the biochemical processes through several theoretically justified and experimentally validated mechanisms [39–43].

One extensively studied and well-established mechanism is based on spintronics. It involves the effect of the weak magnetic fields on the evolving, short-living thermodynamically unstable states of the spin subsystem that can take place in radical chemical reactions, photoluminescence and electron transfer in non-homogeneous magnetic environment [44–49] (Fig. 2a). For several decades researches have focused on the possibility of significantly altering the kinetics and yield of the spin-dependent chemical processes in the liquid and solid phases using weak magnetic fields [44–48]. The effects of such fields on the solid-state quasi-chemical reactions, micro and macro-scale characteristics of the nonmagnetic crystals and polymers and their relaxation processes have been also well documented [50–53]. In these cases due to the lack of thermodynamic equilibrium in the evolving spin and atomic subsystems the weak magnetic field acts as a "catalyst" of sorts. It does not contribute to the total energy of the system but can change the spin state of the short living radical or ion–radical pair and as a result of inter-combinational transitions reduce spin-prohibition to the reaction processes that would not be possible in the absence of the field. Thereby the magnetically induced

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