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Magnetocaloric effect for inducing hypothermia as new therapeutic strategy for stroke: A physical approach

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ABSTRACT

Hypothermia is an effective neuroprotective strategy for acute stroke. However, in clinical practice, the induction of hypothermia is achieved through the systemic reduction of body temperature (using thermal covers or endovascular cooling devices) which results in a complex system associated in many cases to side effects. Therefore, the aim of this study was to test the magnetocaloric effect as a potential new therapeutic strategy for stroke by means of an adiabatic magnetic refrigerator device.

As a first approach, we have developed a simple device to evaluate *in vitro* the thermodynamic behavior of different concentrations of commercial gadolinium powder as a reference magnetocaloric material. The samples, properly thermally insulated, were cyclically magnetized and demagnetized at room temperature by 1 T permanent magnets in order to induce an adiabatic magnetic effect. Under the experimental conditions tested, results showed a maximun non-accumulative temperature variation of 0.2 °C, insufficient to carry out an effective hypothermia. This study allowed us to discuss about the use of new materials and strategies for further *in vivo* experiments.

Introduction

It has been demonstrated that hypothermia is an effective neuroprotective strategy in the management of acute stroke (Azzimondi et al., 1995; Campos et al., 2012; Castillo et al., 1998, 1994). Minutes after the onset of ischemic stroke a cascade of molecular events and cellular processes is triggered, ending up with the destruction of the brain parenchyma hours, days or weeks later. Many of these processes are temperature dependent, so hypothermia represents an ideal neuroprotective therapy, rather than the numerous and unfruitful performed trials with neuroprotective drugs that only block one of the steps of the ischemic cascade (van der Worp et al., 2010). In clinical practice, the induction of hypothermia is achieved through the systemic reduction of body temperature (using thermal covers, immersion in cooling fluids, or endovascular cooling devices) which results in a complex system associated in many cases to severe complications such as, pneumonia and cardiac arrhythmia for instance (Darwazeh and Yan, 2013). However, focal brain hypothermia is an effective and poorly studied therapeutic alternative to systemic hypothermia able to circumvent the harmful side effects associated with systemic cooling. Besides, a localized brain hypothermia treatment would also enable a better patient management and would open the window to design more personalized treatments depending on the patient and lesion characteristics (Castillo et al., 1999; Dong et al., 2001; Krieger et al., 2001; Millán et al., 2008; Schwab et al., 1998; Vila et al., 2000; Yanamoto et al., 1999). Recently, different methods for local brain cooling, such as Peltier chip and headset, have been reported and presented as real alternatives to use in patients (D'Ambrosio et al., 2013; Imoto et al., 2006). Sufficient miniaturization and good performance of the cooling devices were not completely demonstrated and all studies agree that further efforts to develop implantable cooling systems and improve existing ones should be continued.

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In order to find alternative strategies based on focal brain hypothermia, without the secondary side-effects associated to systemic hypothermia, the combination of magnetic nanoparticles and electromagnetic fields (EMF) could constitute a suitable candidate for it. During last decade, magnetic nanoparticles have been applied in biomedicine, such as bioseparation, molecular detection, drug delivery, contrast agents for magnetic resonance imaging and hyperthermia (Wu et al., 2015). These magnetic materials usually are comprised of an iron oxide core with a biocompatible biological polymer. Safety is an issue of constant concern emphasises on the importance of investigating the issue of toxicity, which is highly dependent on the physical, chemical and structural properties of the sample itself as well as dose and intended use. Few *in vitro* studies have reported adverse effects of nanoparticles on cells at *in vitro* in therapeutic doses (Markides et al., 2012). In this line, magnetic and electromagnetic fields are nowadays recognized by medicine as real physical entities that promise the healing of various health problems, especially when conventional medicine has failed (Ross and Harrison, 2015). Magnetotherapy provides a non-invasive, safe and easy approach to directly treat the site of injury and/or the source of pain and inflammation in several diseases (Markov, 2007). It is now commonly accepted that weak electromagnetic fields are capable of initiating various healing processes including delayed fractures, pain relief, multiple sclerosis, and Parkinson's disease (André-Obadia et al., 2006; Fang et al., 2013; VonLoh et al., 2013).

In the present study, magnetic refrigeration, based on the magnetocaloric effect (MCE), is explored as procedure for the generation of focal hypothermia in the brain. MCE is an intrinsic property of magnetic materials. Near the Curie temperature, changes in the magnetization with the applied magnetic field are maximized and induce large variation in the entropy of the magnetic material. In adiabatic conditions, this leads to temperature variations (Clot et al., 2003; Gedik et al., 2009; Gschneidner et al., 2005; Kuhn et al., 2011; Li et al., 2012b; Pecharsky and Gschneidner, 1999, 2001; Tegus et al., 2002). Fig. 1(a) illustrates these behavior represented by adiabatic temperature change, ΔT_{ad}; and isothermal magnetic entropy change, ΔS_M.

In recent years, magnetic refrigeration based on MCE has been greatly developed within the room temperature range for different technological applications (Gedik et al., 2009; Tušek et al., 2009; Yu et al., 2003). However, to the best of our knowledge, this is the first study using the MCE to induce a focal hypothermia for the treatment of stroke. As a first approach, we have developed a simple device to evaluate *in vitro* and *in vivo* the thermodynamic behavior of different concentrations of commercial lanthanide metal gadolinium (Gd) powder as a reference magnetocaloric material. The choice of Gd was based on its second-order paramagnetic–ferromagnetic phase transition at the Curie temperature of 294 K, where the MCE and heat capacity of Gd are maximized as consequence of a large variation of the anisotropy. The fact that this occurs at room temperature in Gd has been the reason by which it has been widely studied in many different applications (Yu et al., 2003). However, during the last decade materials such as $Gd_5(Si_{1-x}Ge_x)_4$, $MnFe(P_{1-x}As_x)$, $La(FeSi)_{13}$ and $Ni_{52}Mn_{34}Sn_{14}$ have been reported to have a large concomitant MCE at the magnetic phase transition, which could be considered in future experiments (Li et al., 2012a,b; Zeng et al., 2011; Zverev et al., 2010).

Materials and methods

Gadolinium

Commercial gadolinium powder (Gadolinium 99%) (Sigma-Aldrich, MO, USA) with the following properties: formula weight = 157.25 g/mol, purity 99% (Based On Rare Earth Analysis) and particle size about 420 μm was chosen for MCE experiments. In order to study the magnetic field dependence of the magnetization for the Gd used, Fig. 1(b) shows the hysteresis curve of this magnetocaloric material as a function of the external applied magnetic field measured in a SQUID magnetometer at room temperature.

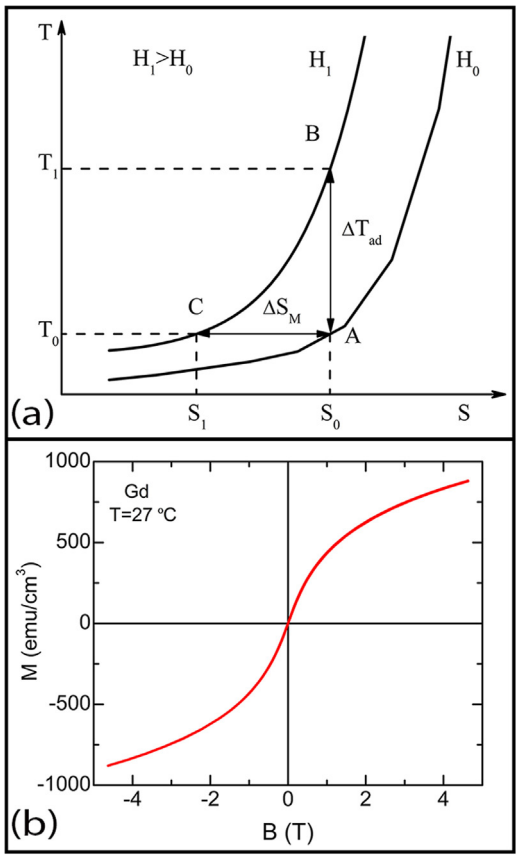

Fig. 1. (a) Temperature-entropy diagram illustrating the magnetocaloric effect (adiabatic temperature change, ΔT_{ab}, and isothermal magnetic entropy, ΔS_M). (b) Hysteresis loop of the Gd powder used in our experiments from −4 to +4 T at room temperature.

Animals

Experimental procedures were approved by the Animal Care Committee of the University Clinical Hospital of Santiago de Compostela according to the Spanish and European Union (EU) rules (86/609/CEE, 2003/65/CE, 2010/63/EU, RD 1201/2005 and RD53/2013). Male *Sprague-Dawley* (SD) rats (Harlan Laboratories, Udine, Italy) with a weight of 380 ± 30 g were used. Rats were watered and fed *ad libitum* with tap water with commercial pellets. The sacrifice was induced by overdose of anesthetic (8% sevoflurane) in a nitrous oxide/oxygen mixture (70/30). After sacrificing the animal, brains were removed and isolated without prior washing. Manipulation of brain tissue was performed using surgical material and PBS (Sigma-Aldrich, MO, USA).

Agar gel phantom and ex vivo *rat brain: thermal behavior comparison*

The thermal behavior of an agar phantom was compared with that from a rat brain in order to use it as *in vitro* model (n = 3). Phantoms were prepared following the method described by Trekker et al. (2014). Briefly, 50–25 ml of liquid 1.6% agar gel (Sigma-Aldrich, MO, USA) was added into falcon tubes of 50 ml, in

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