



# Superparamagnetic iron oxide nanoparticles modified with dimyristoylphosphatidylcholine and their distribution in the brain after injection in the rat substantia nigra

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## ABSTRACT

The subcellular distributions of nanoparticles in the brain are important for their biological application. We synthesized and characterized the superparamagnetic iron oxide nanoparticles (SPIONs) modified with poly (ethylene glycol) (PEG) and polyethylenimine (PEI) (PEG/PEI-SPIONs), and with dimyristoylphosphatidylcholine (DMPC) (DMPC-SPIONs). The nanoparticles were unilaterally injected into the left substantia nigra of rat brains. The distributions of the nanoparticles in the left brains of the rats were examined by ICP-OES (inductively coupled plasma optical emission spectrometer) and TEM (transmission electron microscopy) at 24 h after the injection. Iron was found in the olfactory bulb, temporal lobe, frontal cortex, thalamus and brain stem at 24 h after the injection of DMPC-SPIONs and PEG/PEI-SPIONs. In the rat substantia nigra, most DMPC-SPIONs were distributed in and on the myelin sheath around axons or on cell membranes, some were in cells. As a comparison, less iron was found in the rat brains at 24 h after the injection of PEG/PEI-SPIONs. Our experiments suggest DMPC modification on SPIONs be a safe and effective method for increasing SPIONs distribution on the cell membranes. This work is encouraging for further study on using DMPC-SPIONs for efficient drug delivery or for deep brain stimulation of neurons in a magnetic field.

## 1. Introduction

Superparamagnetic iron oxide nanoparticles (SPIONs) can be used as MRI contrast agents [1,2] and magnetic targeting drug and gene delivery vehicles [3,4]. Iron oxide nanoparticles are also increasingly being used in neurological studies [5], such as magnetic resonance imaging contrast agents for brain amyloid plaques in Alzheimer's disease [6], and collection of neural stem cells in the subventricular zone (SVZ) [7]. It has been recently reported that biological functions can be regulated by the response of magnetic nanoparticles distributed in the brain to the external magnetic field [8–14]. While nanoparticles have shown great potential in biomedical applications [15,16], it is necessary and urgent to study the distribution of nanoparticles synthesized by different methods and modified with different functional groups [6,7,17–19] in vivo, which is influenced by the modification molecules on the surface of nanoparticles and the biological environment [20]. In vitro studies on the distribution of iron oxide nanoparticles in brain cells (glial cells, neurons and neural stem cells) were reported [21]. In vitro incubation of glial cells with iron oxide nanoparticles exhibited

that iron oxide nanoparticles were present in the vesicle structure for > 7 days. The iron oxide nanoparticles did not have a significant impact on glial cell activity although the iron concentration in the glial cells increased 1000 fold [22]. The iron oxide nanoparticles can be decomposed in lysosome by cysteine, ascorbic acid (vitamin C), glutathione and other substances in acidic environment (pH ~ 5) to produce bivalent iron ions, which can be transformed into ferric iron ions by ferritin and stay in ferritin to reduce the harmful iron ions in cells [23]. Albumin modified on iron oxide nanoparticles significantly reduced the amount of iron oxide nanoparticles in glial cells [22,24]. The surface modification of nanoparticles affects their interaction with cells and their distributions [25]. Iron oxide nanoparticles in the body absorb proteins or other biological molecules to form the protein corona, which consists of a relatively stable inner protein layer and an ever-changing outer protein layer formed by certain proteins adsorbed by weak binding forces [26]. Thus, in a time and place-dependent manner, the protein corona determines the fate of iron oxide nanoparticles in the body [22]. Therefore, it is necessary to investigate the in vivo distribution of nanoparticles.

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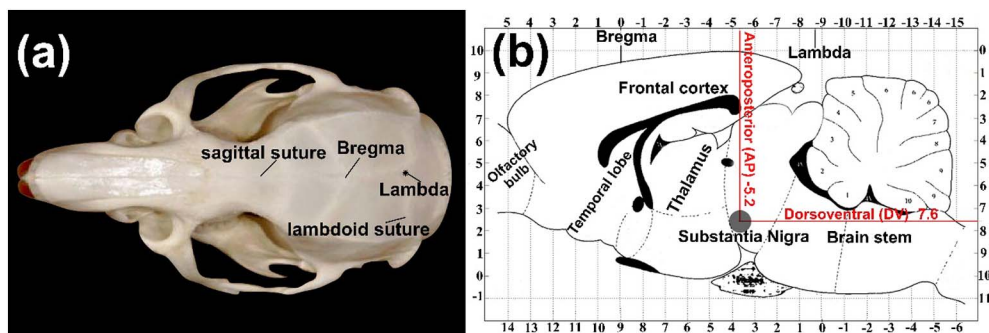


Fig. 1. (a) Rat skull diagram; (b) Sagittal section of the rat brain.

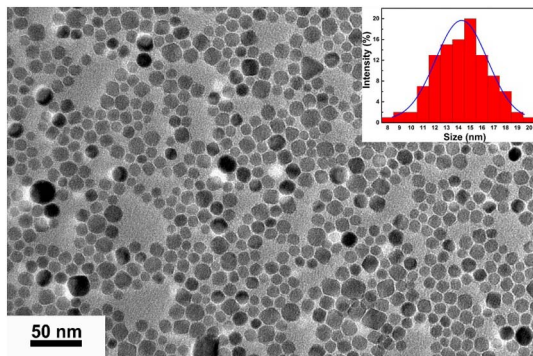


Fig. 2. TEM image and size distribution of DMPC-SPIONs.

Dimyristoylphosphatidylcholine (DMPC) is the main component of cellular membrane and shows excellent biocompatibility [23]. Magnetoliposomes coated with phospholipids were used as targeted drug delivery and hyperthermia agents [27,28]. As a typical phospholipid, DMPC has a long double carbon chain with the zwitterions pair head group containing phosphate and choline. The middle hydrocarbon chains of DMPC are hydrophobic, while the zwitterions pair head groups show perfect hydrophilicity and biocompatibility [29]. DMPCs do not trigger immunological responses, and can escape recognition and elimination by the reticuloendothelial system [30]. SPIONs coated with DMPC, along with poly (ethylene glycol) (PEG) which can reduce the proteins and other biological macromolecules adsorbed on nanoparticles to decrease the immune response that causes cell phagocytosis [31–34], are expected to increase their biocompatibility and to resist the adsorption by proteins and so to increase their half-lives. Few studies [7,11] have been reported on the subcellular level distribution of DMPC modified nanoparticles in brain tissues.

In the present work we conjugated PEG/PEI-modified SPIONs with

DMPC. DMPC-SPIONs and PEG/PEI-SPIONs were injected into the substantia nigra in the brains of Sprague–Dawley (SD) rats. The substantia nigra is a large nucleus in the midbrain, located between the ventral tegmental area and the cerebral pedunculus. Though this method is invasive, the advantage is that the injection amount of the nanoparticles can be adjusted and brain sites for injection of the nanoparticles can be chosen [35]. The distributions of the two differently modified SPIONs in the brain tissue level and in the subcellular level in the brains of rats were investigated and compared.

## 2. Experimental

### 2.1. Preparation of PEG/PEI-SPIONs and DMPC-SPIONs

The raw materials used and the synthesis were reported in our previous published work [1,2]. In brief, PEG/PEI-SPIONs were prepared by the decomposition of 0.7 g of  $\text{Fe}(\text{acac})_3$  (Tokyo Chemical Industry, Japan) in 15.0 g of PEG (Aladdin, China) mixed with 0.3 g of PEI (Aladdin, China) at 280 °C for 1 h in argon atmosphere. The products were washed three times successively with toluene and acetone, and PEG/PEI-SPIONs were collected by setting a magnet under the container. DMPC-SPIONs were prepared by mixing 20 mg of DMPC with 20 ml of 1 mg/ml PEI/PEG-SPIONs dispersed in deionized water. After being shaken together at 4 °C for 5 h, and resting at 4 °C in refrigerator overnight, the mixture was dialyzed against deionized water for 120 h (MWCO 100000 dialysis bag, Spectrumlabs, USA).

### 2.2. Characterization of the SPIONs

The morphology of the nanoparticles was observed under transmission electron microscopy (TEM, JEM-2100F, Japan). The zeta potential and hydrodynamic diameters of the nanoparticles were measured by a Zetasizer Nano ZS90 (Malvern Instruments). Fourier transform infrared spectroscopy (FTIR, Nicolet Nexus 470) and

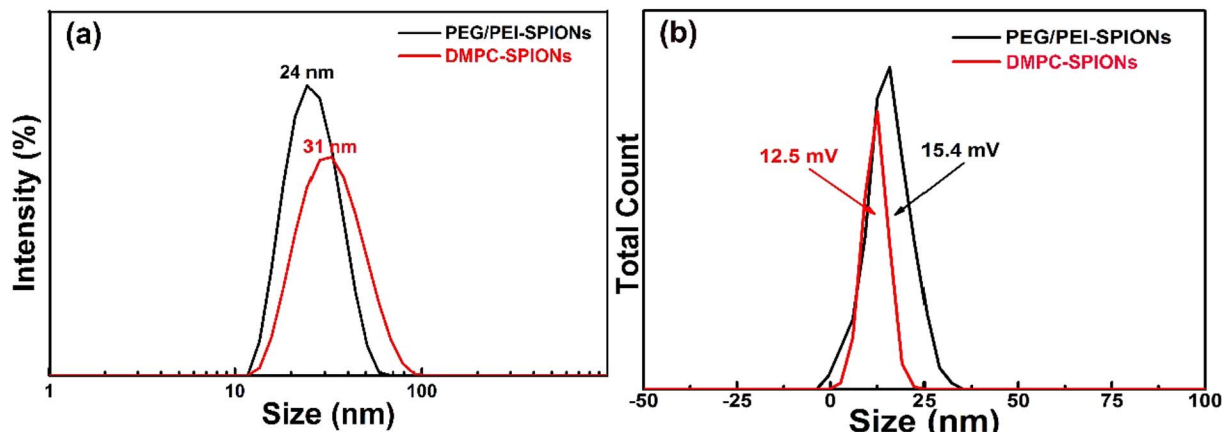


Fig. 3. (a) Hydrodynamic size distribution profiles of PEG/PEI-SPIONs and DMPC-SPIONs, (b) zeta potentials of PEG/PEI-SPIONs and DMPC-SPIONs.

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