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Applications of Magnetic Nanoparticles as Contrast Agents in MRI: Recent Advances and Clinical Challenges

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ABSTRACT

Contrast enhancement agents have been widely used in Magnetic Resonance Imaging (MRI) in clinical diagnostics. Magnetic nanoparticles (MNPs) have shown a promising potential as contrast agent in MRI techniques for in vivo assessments of anatomy, function, and metabolism. This paper aims to systematically review the most common MNPs used as contrast agents for MRI, their contrast enhancing characteristics as well as recent advances and clinical challenges. We searched the PubMed; EMBASE; CINAHL; Web of Science; Google scholar; BIOSIS Previews; Cambridge Scientific Abstracts; and additional sources for published and unpublished papers. The date of the most recent search was 20 July 2015. The keywords were magnetic resonance imaging, contrast agents, nanoparticles, clinical applications, and magnetic nanoparticles. The retrieved results including papers, patents, and books were reviewed and after initial screening were studied and the relevant data were extracted. The main parameters of MNPs, focusing on chemical and physical characteristics influencing the contrast enhancement factor were reviewed and discussed. MRI contrast agents can be divided into two major categories of T1 and T2 contrast agent. Paramagnetic contrast agents are used to enhance contrast in T1 weighted protocols and super paramagnetic contrast agents for T2 weighted protocols. Gadolinium is the most common T1 contrast agents used in MRI. Despite the wide use of Gadolinium, there is serious concern in patients with renal failure. Iron oxide nanoparticles are a good alternative for these patients. However, relaxivity is the main issue when iron oxide is used as contrast agent. The relaxivity strongly depends on the size of nanoparticle. Different types of paramagnetic and superparamagnetic nanoparticles have been developed to overcome the drawbacks associated with gadolinium and iron oxide. However, iron oxide and Gadolinium nanoparticles are still the most common contrast agents in MRI.

Keywords: Magnetic Resonance Imaging, Contrast Agents, Magnetic nanoparticles, Iron oxide, Iron Platinum, Gadolinium, Manganese nanoparticle.

INTRODUCTION

Molecular imaging is a rapidly growing field with the potential to revolutionize cardiovascular imaging through shifting diagnostic focus from functional abnormalities which occur late in a disease process to the biochemical events which precipitate the earliest stages of disease. Advances in nanoparticle technology over the last decade have shown that some of these materials have the potential to play an important role in the diagnosis and treatment of cancers [1-8]. MRI is one of the most useful diagnostic imaging techniques with various applications in clinical medicine because of its excellent spatial resolution, noninvasive and nondestructive nature [9]. Noninvasive study of internal organs of a human body has always been a challenge to medicine [10]. MRI is imaging of soft tissue and in some cases can not generate a sufficient contrast. The development of MRI to one of the most powerful techniques in clinical diagnosis is accompanied by the progress in the design of contrast agents (CAs), which enhance image quality [11]. Magnetic Resonance Imaging contrast agents allow a high sensitivity for the early detection of different pathologies and the tracking of magnetically tagged cells in vivo through molecular and cellular imaging [12]. MRI contrast agents improve diagnostic accuracy in some conditions such as inflammation and infectious diseases of the brain [13], spine [14], and soft tissues [15]. Various contrast agents have been developed for cellular and molecular imaging using MRI [16]. Among the broad spectrum of nanoscale materials being investigated for biomedical applications, Magnetic nanoparticles (MNPs) have gained significant attention due to their intrinsic magnetic properties, which enable tracking through the radiology cornerstone, magnetic resonance (MR) imaging. Currently, contrast agents are used with a diameter of 50 to 350 nm [17]. Today there are great two class of MR contrast agent: T1 and T2 contrast agent. T1 and T2 CAs generate contrast enhancement in MR images via longitudinal and transverse relaxation processes, respectively [18]. The efficiency for MRI CAs consists in lowering the longitudinal (T1) or transverse (T2) relaxation times of the nuclear spins of water protons in tissues [19-21].

2. Basic Principles of Magnetic Resonance Imaging

Magnetic resonance imaging is an imaging modality which is primarily used to construct Images of the NMR signal from the hydrogen atoms in an object. In medical MRI, radiologists are most interested in looking at the NMR signal from water and fat, the major hydrogen containing components of the human body [22]. MRI utilizes the strong static homogenous magnetic field generated by the magnet. When the high frequency magnetic field is applied to the subject placed in the homogeneous static magnetic field, it excites proton nuclear spins within the patient's tissues. The excited proton spins rotate at a rate dependent upon the static magnetic field. As they flip, they emit radio frequency signals, referred as magnetic resonance signals[23]. The signal intensity of a volume element, a voxel, composing the slice depends not only on the quantity of protons present in this voxel but also on the ability the protons have to return to the equilibrium state after being excited with the radio frequency pulse, that means their relaxation properties [24, 25]. The return of excited nuclei from the high-energy state to the low-energy or ground state is associated with loss of energy to the surrounding nuclei [26]. Macroscopically, relaxation can be characterized by the longitudinal return of the magnetization to its ground state in the direction of the main magnetic field. The MR relaxation times include T1 and T2. The T1 longitudinal relaxation time is the time for the magnetization to return to 63% of its original value also is called spin-lattice relaxation. Spins are considered completely relaxed after 3-5 T1 times. T2 is a time at which transversal component has lost 63% of its excited state energy. During this time energy is transported form one spin to nearby spins [27, 28]. For this reason, this decay constant also is named spin-to-spin relaxation. Magnetic resonance imaging (MRI) is a clinical diagnostic modality based on differences in the longitudinal and transverse relaxation rates (1/T1 or 1/T2) of water protons in different tissues [29].

3. Contrast Agents in MRI

MRI signal strength depends on the longitudinal (T1) and transverse (T2) relaxation time of water protons, the difference in the relaxation times causes different contrasts in MRI images [30]. To maximize image quality, MR contrast agents are often needed to decrease T1 and T2 relaxation times [31]. Several materials have been recently developed to enhance the image contrast and diagnostic accuracy of MRI [32-34]. MRI contrast agents can be divided into two main categories of paramagnetic and super paramagnetic compounds. Paramagnetic contrast agents, also called T1 or positive contrast agents, are usually composed of Gadolinium3+ or Mn2+, which generates positive signals on T1-weighted images. Superparamagnetic contrast agents, also called T2 or negative contrast agents, are usually constructed with iron oxide, which generates negative signal on T2 weighted images [35]. T1 contrast agents with reducing spin-lattice relaxation time leads to a stronger signal on T1 weighted images. T2 contrast agents reduce the signal on T2-weighted images by both shortening the spin–spin relaxation time (T2constant) and out-of-phase adjacent protons (by modification of their precession angular velocity). Therefore, magnetic contrast agent, depending on their type, increase the contrast of MRI in molecular level through either increasing (paramagnetic T1contrast agent, mainly Gadolinium-based) or decreasing (superparamagnetic T2 contrast agent, mainly iron-oxide-based) the intensity of MRI signal [36].

4. Paramagnetic Agents

Currently paramagnetic metal ions are used as contrast agents in MRI. These materials are metals with unpaired electrons in their outer shell (transition and lanthanide metals). The two main and widely used compounds of this class are Gadolinium and manganese [37].

4-1. Gadolinium (Gd): Paramagnetic

Different metal ions have been introduced as contrast agents in MRI and the gadolinium (Gd3+) ion is the most commonly used metal ion. This is due to a right combination of large number (seven) unpaired electrons combined with a long electron spin relaxation time which makes this metal a very efficient relaxation enhancing agent [38, 39]. The five MRI contrast agents approved by the FDA are based on Gd(III) ion, the material has high ability to catalyze the relaxation of the water signal and to create positive contrast in MRI [40].

4-1-1.Gd-based magnetic resonance contrast agents (GBCAs) for molecular imaging

- **Gadolinium Gd(III) chelates:** This agent enhances T1 relaxation rate (1/T1) and commonly used as T1 contrast agents, producing a positive image contrast. Because of the toxic even at low concentrations free Gadolinium, it is bound to a chelate **(**usually a low-molecular weight organic molecule such as DTPA5 (diethylene triamine pentaacetic acid)) [41]. Both gadolinium and the ligands alone can't be used because of the toxicity [42]. To date, Gd(III) chelates the property due to strong paramagnetism, strengthening relaxation, stability and inertness in the body, are the most widely used contrast agents in MRI [43]. Gd(III) chelates compound, by altering the relaxation rate of the surrounding water protons to allow for more effective MRI contrast enhancement [40]. The Gd(III) chelate for clinical applications, has been divided into two major groups of cyclic (The macrocyclic ligands, e.g. DOTA and DO3A) and acrylic (The acryclic ligands, e.g. DTPA and DTPA-BMA) [44].
- **Macromolecular Gd(III) complexes:** Small molecular Gd(III) chelates have a relatively low relaxivity and extravasate non selectively from blood into the interstitium of both normal tissue and tumor, which has been a major limitation for their clinical applications. Attaching Gd(III) chelates to macromolecules slows down the rotational motion of the complexes, thus increases relaxivities [45]. For example Gd^{3+}-hexanedione NPs(GdH-NPs) produce stronger signal intensity than Gd-DTPA, probably because the larger Gd complexes with high molecular weight in GdH-NPs cause the slow tumbling rate of GdH-NPs [46]
- **Dendrimer:** Imaging the use of dendrimers as scaffolds to prepare MR contrast agents has received tremendous interest in the scientific community. This is largely due to the well-defined architectures, multivalent surfaces, and nanoscale sizes of dendrimers. Many research groups have explored the use of dendrimers as a new class of T1 positive MR contrast agents [47, 48], Typically Gd(III) complexed with DPTA [49], DOTA [50], or their derivatives for T1 MR imaging applications [51]. Besides the discussed T1 MR contrast agents, dendrimers can also be used as stabilizers to form iron oxide NPs [52].
- **Gadolinium-Based Hybrid Nanoparticles:** recently Gadolinium-based hybrid (GH) nanoparticles were developed as a positive MR contrast agent [53]. Gadolinium-based hybrid (GH) nanoparticles used to blood pool contrast agents. They showed much higher longitudinal relaxivity and transverse relaxivity (r1 and r2) than Gd–DTPA which are commonly used for clinical magnetic resonance imaging. The GH nanoparticles can use as liver specific contrast agent [54]. Luminescent hybrid nanoparticles with a paramagnetic Gd_2O_3 core were also applied as contrast Agents for magnetic resonance imaging. These particles can be followed up by fluorescence imaging [55] .
- **Biodegradable macromolecular:** These new agents can act as macromolecular contrast agents for in vivo imaging and excrete rapidly as low molecular- weight agents. The polydisulfide Gd(III) is a biodegradable macromolecular, complexes have a great potential to be developed as safe, effective, biodegradable macromolecular MRI contrast agents for clinical applications [56, 57].
- **Liposomal particles:** Gd(III) complexes including Gd-DTPA [58, 59], Gd(DTPA-BMA) [60] and Gd-DOTA [61] have been encapsulated in the core of liposomes to prepare nano-scaled MRI contrast agents [62].
- **Targeted contrast agents:** The use of targeted contrast agents can improve contrast and provide information about specific biomarkers [63, 64], (e.g. Tumor-targeting with small molecular, protein, dendrimer, liposomal-based Gd contrast agents) [43].

4-1-2.Types of gadolinium contrast agents:

Gadolinium (III) contrast agents can be divided into three groups of the extracellular fluid agents, blood pool and organ-specific agents.

Extracellular fluid agents: Dotarem, Magnevist, Omniscan, OptiMARK, and Prohance are some of these compounds [65]. When these agents are intravenously injected, randomly distribute within the vascular and interstitial ECF space and then excreted rapidly in their unchanged forms through the kidney glomerular filtration in the kidney [42]. All approved GBCAs are administered intravenously, distribute into accessible extracellular spaces with a distribution half-life about 10 min, and are excreted through the kidneys with a plasma half-life typically about 90 min in healthy human adults [66]. In case of malfunction of the kidneys, contrast agent plasma elimination can be Considerably prolonged, with a half-life that may exceed 30 hour in some individuals [67].

Blood pool agents (intravascular agents): The first-generation MR contrast agents was based on this design and have been used to image ruptures in the blood–brain barrier(BBB) [68]. This unique type of contrast agents refers to a diversity of contrast agents that are confined by purpose to the intravascular space and allocated exclusively to cardiovascular applications [69]. This property of blood-pool (BP) can be find out by controlling the distribution and elimination of the contrast agents, which in turn by their size relative to the permeability of the capillary endothelium in various organs determined. Although BP contrast agents are limited partially or entirely in passing through the endothelial membrane bound, they can still be excreted through the kidneys [42].These agents are designed in two ways: by connecting the Gd^{3+} ions to a macromolecular polymer formed during the synthesis [70] or combination of Gd^{3+} with plasma proteins to form macromolecules in blood after injection [71]. Modification the structure of polydifulfide Gd(III) complexes can lead to biodegradable macromolecular contrast agents with various reinforce profiles in the blood pool. Polydisulfide Gd(III) complexes have relatively long blood circulation time are gradually into small compounds that are rapidly excreted through the kidney filtration converted. The use of biodegradable macromolecular contrast agents in MRI imaging cardiovascular disease and cancer, and to evaluate the response to treatment [72-74].

Organ-specific agents: Organ-specific agents are designed to specifically accumulate in a given organ or tissue. The diagnosis of hepatic lesions continues to be a problem even though many diagnostic methods are available [75]. Although the more commonly used MR contrast media are gadolinium (Gd) chelates, they are relatively non-specific due to the rapid accumulation in the liver [76]. Many efforts have been made to serve Gd3+as specific contrast agents, small unilamellar liposomes used as carriers for gadolinium chelates. This chelates Trap in aqueous volume of liposomes and has the potential not only as a specific contrast agent for the liver and spleen, but also for imaging vascular system [77]. Tetra-*P*-aminophenylporphyrin (TPP) was conjugated with gadolinium diethylenetriaminepen-taacetic acid (DTPA) (Gd2(DTPA)4TPP) could be a useful in MR imaging contrast agent with an specific tumors contrast agent [78]. A new class of metal-loaded nanoparticles has developed that have potential as contrast agents for medical imaging. In this case, the nanoparticles are loaded with Gd3+ to provide contrast in magnetic resonance (MR) imaging. The Gd3+-loaded nanoparticles have a diameter of 120 nm, and provide excellent contrast when used to image the heart and gastrointestinal tract in a rat animal model [79].

4-1-3. Safety of gadolinium contrast agents

One of the important properties of MRI contrast agents in clinical uses is safety. Because Gd(III) ions are very toxic in ionic form, extremely interfering with calcium channels and protein binding sites, they cannot be administered directly [80, 81]. Free Gd ions accumulate in the liver, spleen, kidney, and bones. To reduce the side effects of toxic ions and prevent tissue interaction, Gd(III) ions are combined with chelating ligands. but Toxic Gd(III) ions may still be released of some chelates via transmetallation with other metal ions such as Zn2+, Ca2+ and Cu2+ in the body and protonation of the ligands in the pH low which may cause the separation of scheelite within the body [82, 83]. Nephrogenic fibrosing dermopathy (NFD) is an idiopathic disorder in Kidney patients. In most patients with NFD, dialysis for kidney failure occurs [84, 85].It often affects middle-aged. The Gd–DTPA is a small compound that is easily released from the pores of the vessels. Gd-containing contrast agents in patients with normal kidney function are rapidly excreted from the kidney with a half-life of about 2 hours, however, in patients with chronic renal failure have a long half-life, and may be greater than 120 to 30 hours. If immediate after MR angiography dialysis be inadequate markedly prolongs Gd clearance [86]. The combination of metabolic acidosis and insufficient clearance of Gd-containing agent is present in renal failure [87, 88]. patient dehydration, advanced age, use of concomitant nephrotoxic drugs, multiple myeloma, heart failure, and liver disease are other risk factors [89-92].

CONCLUSION

The use of contrast agents has revolutionized MRI technique especially in molecular imaging. Improvements in the stability, relaxivity, safety and other characteristics of contrast agents make MRI a powerful tool for the diagnosis of abnormalities of the soft tissue. Today, Gadolinium nanoparticles are used as contrast agent to improve image quality of MRI technique. Despite plenty of research has been conducted on Gadolinium, there is serious concern in patients with renal failure. Iron oxide nanoparticles are a good alternative for these patients. Relaxivity is problematic when the iron oxide is used as contrast agent, because this factor strongly depends on the size of nanoparticle. However, other types of paramagnetic and superparamagnetic nanoparticles have been developed to overcome these weaknesses, but still iron oxide and Gadolinium nanoparticles are the most common contrast agent in MRI.

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