Research progress of magnetic resonance imaging contrast agents

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Abstract  Magnetic resonance imaging (MRI) is a clinical diagnostic modality, which has become popular in hospitals around the world. Approximately 30% of MRI exams include the use of contrast agents. The research progress of the paramagnetic resonance imaging contrast agents was described briefly. Three important approaches in the soluble paramagnetic resonance imaging contrast agents design including nonionic, tissue-specific and macromolecular contrast agents were investigated. In addition, the problems in the research and development in future were discussed.

Keywords: magnetic resonance imaging (MRI), contrast agents, gadolinium(III) complexes, tissue-specific.

Developed in 1973 by Paul Lauterbur[1], magnetic resonance imaging (MRI) has become popular in hospitals around the world since it received FDA approval for clinical use in 1985. MRI is a clinical diagnostic modality, which relies on the detection of NMR signals emitted by hydrogen protons in the body placed in a magnetic field. It can detect and characterize necrotic tissue, infarcted artery and malignant diseases such as tumors[2] etc.

Currently, approximately 30% of MRI exams include the use of MRI contrast agents. MRI contrast agent is a diagnostic agent that could be administered to a patient in order to change the relaxation rates of the water protons in tissues, shorten the longitudinal (or spin-lattice) relaxation times, $T_1$, and the transverse (or spin-spin) relaxation times, $T_2$, of protons in tissues in which the agent accumulates, enhancing the image contrast between normal and diseased tissues and indicating the status of organ function or blood flow[3].

1 The research background in MRI contrast agents

Aside from standard biocompatible pharmaceutical features such as water solubility and shelf stability, MRI contrast agents should be safe, have higher relaxivity, good contrast-enhancing properties, some specific in vivo distribution and longer intravascular duration and excre­tability within hours of administration.

In the research field of MRI contrast agent, superparamagnetic iron oxide particles and soluble paramagnetic metal complexes are two critical developments in MRI contrast agents. Superparamagnetic iron oxide agent consists of specific crystal Fe$_3$O$_4$ structure core particles with coating materials, such as dextran, polysaccharide, and polystyrene.

The soluble paramagnetic metal complex contrast agents are composed of ligands and paramagnetic metal ions, including Fe$^{2+}$, Fe$^{3+}$, Mn$^{2+}$, Gd$^{3+}$ and Dy$^{3+}$. Gadolinium(III) ion is a good paramagnetic metal ion, for it has seven unpaired electrons, the symmetric electronic states, high relaxivity and a total coordination number of nine. However, some of free ligands and Gd$^{3+}$ lead to disruption of critical Ca$^{2+}$-required signaling and tend to be toxic in body.

So proper ligands are chosen and chelated with Gd$^{3+}$ to form complexes strong enough that they actually remain chelated in the body and are excreted intact. Polyaminocarboxylates, such as diethylenetriaminepentaacetic acid (DTPA), 1,4,7,10-tetraazacyclododecane-N,N',N",N"~ tetraacetic acids (DOTA), ethylene diamine tetraacetic acid (EDTA) and their derivatives (fig. 1), have been the main choices of these off-the-shelf ligands.

The gadolinium(III) chelates such as Gd-DTPA (Magnevist$^4$), Gd-DTPA-BMA(Omniscan$^5$), Gd-D03A-HP (Prohance$^6$) and Gd-DTOA (Dotarem$^7$) (fig. 1) have been approved for clinical use. Several introductory and review articles are available, covering the theory, structure, dynamics, design, and applications of gadolinium(III) chelates as MRI contrast agents$^{8,9}$. The research progress of the soluble paramagnetic metal complex MRI contrast agents is only discussed in detail in this review now.

2 Research progress of MRI contrast agents

In recent years, one important approach in the research and development of paramagnetic metal complex contrast agents is that Gd-DTPA and Gd-DOTA are modified to prepare a series of MRI contrast agents$^{10}$. It in...
includes three directions as follows.

(i) Nonionic contrast agents. Gd-DTPA is a low molecular weight and ionic complex. After injection, the agent distributes nonspecifically throughout the plasma and interstitial space of the body and excreted by the kidney. The injection of large quantities of the ionic complex can raise the in vivo ion concentration and cause localized disturbances in osmolality, which, in turn, can lead to cellular and circulatory damages.

Gd-DTPA and Gd-DOTA are modified to form neutral molecules, which thus exhibit much lower osmolality, while these neutral agents have been shown to have higher LD₅₀s in animals. Gd-DTPA-BMA and Gd-DOTA-HP have been nonionic contrast agents commercially available for clinical use.

A series of DTPA derivative ligands containing bulky alkyl and aryl side chains have been synthesized by the reaction of DTPA dihydrazide with alkylol, arylol, amine, amino acid or peptide. Compared with Gd-DTPA, their non-ionic bulky Gd³⁺ complexes have higher relaxivities and lower stability constants[11-16].

(ii) Tissue-specific contrast agents. Some tissue-specific groups were incorporated into Gd-DTPA and Gd-DOTA to obtain the tissue-specific contrast agents, such as liver-targeting agents, tumor-targeting agents and blood pool agents.

The effective way to obtain some hepatobiliary excretion of small-molecular-weight contrast agents is to increase the lipophilicity of Gd-DTPA, for example, by adding aromatic rings to the chelates[17]. Hepatobiliary Gd-DTPA derivatives include gadobenate dimeglumine (Gd-BOPTA)[18] and gadolinium ethoxybenzyltrimamine pentaacetic acid (Gd-EOB-DTPA)[19], which are considered to be taken up in the hepatocyte and be excreted in the bile (fig. 2).

It is known that there exist a large number of asialoglycoprotein receptors on the surface of mammalian hepatocytes which can selectively recognize, bind to galactose-terminated glycoproteins and internalize them by a receptor-mediated endocytosis process[20]. Hepatobiliary derivatives of Gd-DTPA and Gd-DOTA containing galactose moiety were synthesized[21, 22]. Other liver-targeting chelates of DTPA derivatives with Gd³⁺ and Mn²⁺ containing vitamin B₆ moiety were prepared, too[23].

Manganese dipyradoxyl-diphosphate (Mn-DPDP) is a contrast agent developed for imaging of the hepatobiliary system (fig. 3). Unlike Gd-DTPA, Mn-DPDP is an intracellular agent that is taken up specifically by hepatocyte and pancrea, and excreted in the bile. The ligand consists of two linked pyridoxal-5'-phosphate groups, and the catalytically active form of vitamin B₆. Thus someone thought that Mn-DPDP is a potential candidate for specific hepatocyte uptake by the pyridoxine transporter at the sinusoidal pole; however, someone reported that the complex dissociates both in the blood and in the liver and the uptake of Mn-DPDP does not depend on the pyridoxine transporter[24].

Manganese porphyrins and other soluble metalloporphyrins have been used as the tumor-targeting MRI agents for tumor detection because of the nonspecific binding of porphyrins to the interstitial space in tumors[25, 26]. Texaphyrins, such as PCI-0120 Gd³⁺ (bistriethylene glycol gadolinium texaphyrin diacetate), are bigger than the average porphyrin and take advantage of porphyrins’ specificity for tumors (fig. 4). Gadolinium texaphyrins can bind four to five water molecules in the gadolinium inner coordination sphere, and possess high relaxivity. Thus gadolinium texaphyrins can be useful for detecting small tumors.

Some folate binding proteins exist in both the serum of patients with cancer and on the cell surface of many human cancers of epithelial origin. Thus the folate-conjugated gadolinium complexes can be taken up specifically by tumor cells, and increase the longitudinal relaxation rates of tumor cells[27].

MP-2269 (4-pentylbicyclo[2.2.2]octane-1-carboxyl-di-L-aspartyl-lysine-derived-DTPA gadolinium complex) is a nonaromatic small-molecule MRI contrast agent. Proton relaxometry studies in vitro yielded spin-lattice relaxivities (R₁) for MP-2269 of 6.2, 20.0 and 26.1 (mmol/L)⁻¹ • s⁻¹ in water, rabbit blood, and human blood, respectively. The enhanced relaxivities in blood indicate significant binding of the agent to blood proteins. MR imagings and biodistribution studies in rats showed that MP-2269 has potential for future exploitation as an efficacious blood pool agent[28].

(iii) Macromolecular conjugates. Macromolecular MRI contrast agents usually exhibit more effective relaxation than that of the low molecular weight metal complex alone and improve the relaxivity of per gadolinium atom since an increase in rotational correlation time. On the other hand, a macromolecular MRI contrast agent may show prolonged intravascular retention due to its bulky molecular volume, it can be used clinically as a blood pool contrast agent[29]. In addition, when an organ-targeting group is attached to this macromolecular metal complex, it can be endowed with tissue-targeting property.

![Fig. 2. The structural formulae of EOB-DTPA and BOPTA.](image-url)