Ferumoxides

SSPIO

Kam Leung, PhD[1]

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Chemical name:	Ferumoxides	
Abbreviated name:	SSPIO	
Synonym:	Dextran-coated superparamagnetic iron oxide, AMI-25, SHU 555A	
Agent Category:	Superparamagnetic Iron Oxide	
Target:	Reticuloendothelial system	
Target Category:	Internalized by phagocytes	
Method of detection:	Magnetic Resonance imaging (MRI)	
Source of signal\contrast:	Iron oxide	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans	No structure is available in PubChem.

Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally. Protons (hydrogen nuclei) are widely used to create images because of their abundance in water molecules. Water comprises about 80% of most soft tissues. The contrast of proton MRI depends mainly on the density of nuclear (proton spins), the relaxation times of the nuclear magnetization (T1, longitudinal and T2, transverse), the magnetic environment of the tissues, and the blood flow to the tissues. However,

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

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insufficient contrast between normal and diseased tissues requires the development of contrast agents. Most of the contrast agents affect the T1 and T2 relaxation of the surrounding nuclei, mainly the protons of water. T-2* is the spin-spin relaxation time composed of variations from molecular interactions and intrinsic magnetic heterogeneities of tissues in the magnetic field (1).

Superparamagnetic iron oxide (SPIO) structure is composed of ferric iron (Fe^{3+}) and ferrous iron (Fe^{2+}) in the general formula of $Fe_2^{3+}OFe^{2+}O$. The iron oxides particles are coated with a layer of dextran or other polysaccharide. These particles have a large combined magnetic moments or spins which are randomly rotated in the absence of an applied magnetic field. SPIO is used mainly as a T2 contrast agent in MRI though it can shorten both T1 and T2/T2* relaxation processes. SPIO particle uptake into the reticuloendothelial system (RES) is by endocytosis or phagocytosis. SPIO particles are taken up by phagocytic cells such as monocytes, macrophages, and oligodendroglial cells. A variety of cells can also be labeled with these particles for cell trafficking and tumor-specific imaging studies. SPIO agents are classified by their sizes with coating material (about 20 nm to 3,500 nm in diameters) as large SPIO agents (Ferumoxsil or AMI-121, Ferucarbotran, OMP), standard SPIO (SSPIO) agents (Ferumoxides or AMI-25, SHU 555A), ultrasmall SPIO (USPIO) agents (Ferumoxtran or AMI-277, NC100150) and monocrystalline iron oxide nanoparticles (MION) agents (1).

Ferumoxides are composed of iron particles of about 5 nm, and the hydrodynamic diameter is about 80-150 nm. The crystals are covered with a layer of dextran. Ferumoxides are classified as SSPIO. Ferumoxides have been tested in clinical trials as negative contrast agents that decrease signal on T2 images. Ferumoxides have been used in liver, spleen, and myocardial perfusion MR imaging (1).

Synthesis

[PubMed]

SPIO agents are produced by controlling the precipitation of iron oxide in an aqueous solution of ferric salt, ferrous salt, and coating material by addition of an alkaline solution while active stirring or sonication is applied. The desired SPIO size of the agent is isolated and purified by differential column chromatography, centrifugation, and dialysis. Electron microscopy, X-ray diffraction and laser light scattering are used to measure median diameter of the nanoparticles. Relaxivities are measured by NMR spectroscopy (1).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

It was shown that the uptake of SPIO by human monocytes was dependent on size, concentration, and time. SSPIO uptake was higher than USPIO uptake as measured by iron content and T2* relaxivity. The uptakes of both were directly proportional to concentration and time. The surface property of SPIO is also an important factor (2) (3).

In the presence of polyinosinic acid or fucoidan (specific ligands of scavenger receptors SR-A types I and II), the endocytosis of AMI-25 by mouse peritoneal macrophages was inhibited in a dose-dependent manner. Without competitors, uptake of AMI-25 by mouse peritoneal macrophages ranged between 3% and 8%. On human activated monocyte THP-1 cell assay, AMI-25 showed a higher macrophage uptake (between 1.1 and 3%) compared with USPIO (between 0.03 and 0.12%). This difference is attributed to the larger size of AMI-25 nanoparticles (2).

Animal Studies

Rodents

[PubMed]

The blood half-life of USPIO (the hydrodynamic diameter is about 11 nm) in rats was 81 min, considerably longer than that of larger SPIO preparations, such as AMI-25 (6 min). AMI-25 showed a rapid clearance by the liver and spleen, with no detectable uptake in the lymph nodes. Peak concentrations of iron were found in the liver after 2 h and in the spleen after 4 h. Iron was cleared slowly from the liver and spleen with a half-life of 3 and 4 days, respectively (4). Myocardial T2-weighted signal decreased in rat hearts after AMI-25 infusion in normal rats. The intensity remained constant in the rat heart transplants during coronary occlusion, both before and after the infusion of AMI-25 and decreased further upon reperfusion. Therefore, AMI-25 is able to identify normal, ischemic, and reperfused myocardium (5).

Atherosclerotic plaques in cytokine-treated mice contained more iron-positive macrophages per cross section than did those in sham-treated control mice. Iron-laden macrophages were present either in subendothelial plaque surfaces or in thin layers overlying the internal elastic lamina, often at the edges of atherosclerotic plaques. No iron deposition was seen in aortas of the wild-type, non-atherosclerotic control mice. Immunocytochemistry showed mostly macrophages and few T lymphocytes in atherosclerotic plaques of cytokine-treated mice (6).

Bos et al. (7) were able to track intravascularly injected, ferumoxide-labeled mesenchymal stem cells in rat kidney and liver using *in vivo* MRI T2* measurements. The labeled cells were able to differentiate into adipocytes and osteocytes in cultures. The cells were detected up to 7 days in the kidney and 12 days in the liver. Immunohistochemical analysis results confirmed these mesenchymal stem cells in renal glomeruli and hepatic sinusoids. Additional studies are needed to evaluate stem cell differentiation and to assess resultant cellular function *in vivo* in the target organs.

Other Non-Primate Mammals

[PubMed]

Rabbits were injected with SPIO nanoparticles to evaluate liver localization and magnetic resonance appearance. Small (30 nm), standard (300 nm) and large SPIO particles (3,500 nm) reduced the T2 of liver by 50%, 40% and 15%, respectively, and the T2 of spleen by 60%, 65%, and 25%, respectively, at 1 mg Fe/kg intravenous injection. Both small and standard SPIO nanoparticles decreased the T1 of spleen by 35%, with no effect on liver T1. Magnetic resonance imaging showed decreased signal intensity ratios by 80% and 60% for small and standard SPIO nanoparticles, respectively (8).

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Ferumoxides-enhanced MR imaging significantly increases tumor/liver contrast and improves tumor lesion recognition on T2-weighted images (9). A 95% sensitivity for metastatic tumor detection was reported by using ferumoxides-enhanced MR imaging (10). In a large multi-center trial, additional liver tumors were identified on 27% of ferumoxides-enhanced images compared with non-enhanced images (11). The major potential applications for ferumoxides are as (a) an intravenous contrast agent for the liver [PubMed], (b) a spleen contrast agent [PubMed], (c) a perfusion agent for the heart [PubMed], and (d) a monitoring agent for macrophage infiltration in pathological tissues [PubMed].

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