Octreotide conjugated to pegylated ultrasmall superparamagnetic iron oxide nanoparticle

USPIO-PEG-OCT

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Chemical name:	Octreotide conjugated to pegylated ultrasmall superparamagnetic iron oxide nanoparticle	
Abbreviated name:	USPIO-PEG-OCT	
Synonym:		
Agent category:	Peptide	
Target:	Somatostatin receptors (SSTRs)	
Target category:	Receptor	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal:	Iron oxide	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about somatostatin.

Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally. Protons (hydrogen nuclei) are widely used in imaging because of their abundance in water molecules. Water comprises ~80% of most soft tissue. The contrast of proton MRI depends primarily on the density of the nucleus (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, insufficient

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contrast between normal and diseased tissues requires the development of contrast agents. Most contrast agents affect the T1 and T2 relaxation times of the surrounding nuclei, mainly the protons of water. T2* is the spin–spin relaxation time composed of variations from molecular interactions and intrinsic magnetic heterogeneities of tissues in the magnetic field (1). Cross-linked iron oxide (CLIO) nanoparticles and other iron oxide formulations affect T_2 primarily and lead to decreased signal. On the other hand, the paramagnetic T_1 agents, such as gadolinium (Gd^{3+}), and manganese (Mn^{2+}), accelerate T_1 relaxation and lead to brighter contrast images.

The superparamagnetic iron oxide (SPIO) structure is composed of ferric iron (Fe^{3+}) and ferrous iron (Fe^{2+}). The iron oxide particles are coated with a protective layer of dextran or other polysaccharide. These particles have 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 reticuloendothelial system (RES) is by endocytosis or phagocytosis. SPIO particles are also 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 (~20–3,500 nm in diameter) as large SPIO (LSPIO) nanoparticles, standard SPIO (SSPIO) nanoparticles, ultrasmall SPIO (USPIO) nanoparticles, and monocrystalline iron oxide nanoparticles (MION) (1).

Somatostatin (SST) is an inhibitor of the release of somatotropin, glucagon, insulin, gastrointestinal hormones, and other secretory proteins (2). SST is also known as somatotropin release-inhibiting factor (SRIF). SST is a cyclic polypeptide with two biologically active isoforms (SRIF-14 and SRIF-28) of 14 and 28 amino acids. SST has a short plasma half-life of <3 min (3). Critical to these actions is the expression of SS receptors (SSTRs) present on cells. SSTRs (G-protein coupled) have been found on a variety of neuroendocrine tumors and cells of the immune system, and five individual subtypes (sst_1-sst_5) have been identified and subsequently cloned from animal and human tissues (4, 5). ^{111}In-DTPA-octreotide (^{111}In-DTPA-OC) is a SSTR analog that, over the last decade, has remained the most widely used radiopharmaceutical for the scintigraphic detection and staging of primary and metastatic neuroendocrine tumors bearing SSTRs with Single-photon emission computed tomography (6). It has also showed promising results in peptide-receptor radionuclide therapy (7). ^{111}In-DTPA-OC binds with high affinity to SSTR subtypes 2 and 5 (sst_2 and sst_5) and to sst_3 to a lesser degree but does not bind to sst_1 and sst_4 (8). USPIO is composed of iron nanoparticles of 4–6 nm diameters and the hydrodynamic diameter with polyethylene glycol (PEG) coating is 20–50 nm. USPIO nanoparticles have a long plasma half-life because of their small size. The blood pool half-life of plasma relaxation times is calculated at ~24 h in humans (9) and 2 h in mice (10). Because of its long blood half-life, USPIO can be used as blood pool agent during the early phase of intravenous administration (11). In the late phase, USPIO is suitable for the evaluation of RES in the body, particularly in lymph nodes (12). Li et al. (13) conjugated OCT to USPIO-PEG to form USPIO-PEG-OCT for MRI of SSTRs in tumor.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (Somatostatin receptors, Somatostatin).
- Articles in OMIM
- Clinical trials (Somatostatin receptor)
- Drug information in FDA (Somatostatin receptor)

Synthesis

[PubMed]

A solution of OCT (0.8 mg) was added to a mixture of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (5 μmol), N-hydroxysulfosuccinimide (12.5 μmol) and USPIO-PEG nanoparticles (0.8 mg) (13). The pH of the solution was adjusted to 7.5 using NaOH. USPIO-PEG-OCT had a hydrodynamic size of 20 nm. The number of Oct peptides per USPIO-PEG was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Li et al. (13) performed *in vitro* uptake studies of USPIO-PEG-OCT and USPIO-PEG (10 μg Fe/ml) in cultured human breast adenocarcinoma MCF-7 cells, which was shown to express SSTRs. A strong uptake of USPIO-PEG-OCT was observed at 12 h after incubation as measured with histological staining of Fe, whereas there was not uptake for USPIO-PEG. Excess OCT was able to block the uptake of USPIO-PEG-OCT. T2-weighted imaging showed that the T2 values of the cells (n = 6/group) incubated with USPIO-PEG-OCT, USPIO-PEG, and buffer were 56.6 ± 13.1, 75.4 ± 16.2, and 86.0 ± 22.4 s, respectively. USPIO-PEG-OCT exhibited a higher negative enhancement of USPIO-PEG-OCT than USPIO-PEG on MCF cells. There were statistically significant differences ($P < 0.05$) between USPIO-PEG-OCT and USPIO-PEG, and between USPIO-PEG-OCT and buffer. USPIO-PEG-OCT had no effect on the viability of MCF-7 cells in culture up to 80 μg Fe/ml at 12 h of incubation and 20 μg Fe/ml up to 96 h of incubation.

Animal Studies

Rodents

[PubMed]

USPIO-PEG-OCT or USPIO-PEG (7.7 mg Fe/kg) were injected intravenously in the mice bearing MCF-7 tumors ($n = 12$ mice/group) (13). T2-weighted MR images (3 T) of the tumors were obtained at 0-24 h after injection. There was a loss of signal intensity of 24.49% and 19.81% for USPIO-PEG-OCT and USPIO-PEG at 6 h after injection ($P < 0.05$), respectively. Both nanoparticles exhibited little loss of signal by 24 h after injection.

Histological staining of Fe in tumors showed that there was a large amount of Fe in the tumor tissues of USPIO-PEG-OCT treated mice but not in the tumor tissues of USPIO-PEG treated mice at 6 h after injection. No blocking experiment was performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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