Ultrasmall superparamagnetic iron oxide nanoparticles conjugated with Ile-Pro-Leu-Pro-Phe-Tyr-Asn

USPIO-PHO

Kam Leung, PhD[1]

Created: February 23, 2010; Updated: March 25, 2010.

Chemical name:	Ultrasmall superparamagnetic iron oxide nanoparticles conjugated with Ile-Pro-Leu-Pro-Phe-Tyr-Asn	
Abbreviated name:	USPIO-PHO	
Synonym:		
Agent category:	Peptide	
Target:	ß-amyloid ($A\beta_{42}$) peptide	
Target category:	Acceptor	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal:	Iron oxide	
Activation:	No	
Studies:	• *In vitro* • Rodents	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, which comprise >80% of most soft tissues. The contrast of proton MRI images depends mainly on the density of nuclear (proton spins), the

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

Corresponding author.

NLM Citation: Leung K. Ultrasmall superparamagnetic iron oxide nanoparticles conjugated with Ile-Pro-Leu-Pro-Phe-Tyr-Asn. 2010 Feb 23 [Updated 2010 Mar 25]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

relaxation times of the nuclear magnetization (T1, longitudinal; T2, transverse), the magnetic environment of the tissues, and the blood flow to the tissues. However, insufficient contrast between normal and diseased tissues requires the use of contrast agents. Most contrast agents affect the T1 and T2 relaxation 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) and other iron oxide formulations affect T2 primarily and lead to a decreased signal. On the other hand, the paramagnetic T1 agents, such as gadolinium (Gd^{3+}), and manganese (Mn^{2+}), accelerate T1 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 molecular 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).

Alzheimer's disease (AD) is a major neurodegenerative disease associated with an irreversible decline of mental functions and with cognitive impairment (2). It is characterized pathologically by neuronal loss with the presence in the brain of senile plaques of β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles of filaments that contain the hyperphosphorylated protein tau (3, 4). Accelerated deposition of Aβ deposits seems to be a key risk factor associated with AD. Early diagnosis of AD is important for treatment consideration and disease management (5). Several radioligands for positron emission tomography have been developed (6-8) and tested in humans as *in vivo* diagnostic tools for molecular imaging and measuring the formation of Aβ deposits (8). USPIO is composed of iron nanoparticles 4–6 nm in diameter, and the hydrodynamic diameter with polyethylene glycol or dextran 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 a 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). A cyclic peptide, Cys-Ile-Pro-Leu-Pro-Phe-Tyr-Asn-Cys, was identified with phage screening against $A\beta_{42}$ peptide (13). Ile-Pro-Leu-Pro-Phe-Tyr-Asn (PHO) was synthesized and conjugated to dextran-coated USPIO to form USPIO-PHO for MRI of $A\beta_{42}$ in the brain.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (Amyloid).
- Articles in OMIM
- Clinical trials (Amyloid)
- Drug information in FDA (Amyloid inhibitors)

Synthesis

[PubMed]

PHO peptide was linked covalently to USPIO with the reactive alkyl halogen end of epichlohydrin binding to the hydroxyls of dextran coating of Fe_3O_4 particles (USPIO) to obtain a terminal glycidyl ether derivatives, which were then reacted with the amine group of the peptide (13). Longitudinal (r_1) and transverse (r_2) relaxivities (nuclear magnetic resonance (NMR) efficiency expressed in $s^{-1}mM^{-1}$) of USPIO-PHO were measured at 37°C and 20 MHz (r_1 = 32.26, r_2 = 85.32, and r_2/r_1 = 2.64) and 60 MHz (r_1 = 13.50, r_2 = 83.75, and r_2/r_1 = 6.20). The number of PHO peptides per USPIO was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Larbanoix et al. (13) performed *in vitro* binding of USPIO-PHO to mouse $A\beta_{42}$. USPIO-PHO had a binding affinity of 0.12 nM as determined with NMR relaxometry. USPIO did not bind to mouse $A\beta_{42}$.

Animal Studies

Rodents

[PubMed]

Larbanoix et al. (13) performed *ex vivo* biodistribution in rats (n = 3/group) after injection of UPSIO-PHO or USPIO. UPSIO-PHO (0.1 mmol Fe/kg) had a blood half-life for elimination of 779 min, which was longer than that of USPIO (255 min). A majority of iron was found in the lungs and liver for both nanoparticles. There was a significant contrast enhancement of USPIO-PHO in the brain compared to USPIO ($P < 0.05$). In another experiment, USPIO-PHO nanoparticles (0.08 mmol Fe/kg) were injected intravenously to a double transgenic APP/PS1 mouse after injection of 25% mannitol to open up the brain–blood barrier. MRI imaging was performed at 4.7 T. There was a signal decrease of 48% in the cortex and striatum areas at 9 min, and the signal stayed constant up to 87 min after injection of the nanoparticles. In contrast, there was only ~15% maximum signal decrease in these brain areas in the wild-type mouse at 32 min after

injection. Histological staining of Fe in the brain sections of APP/PS1 mice showed that there was a large amount of Fe in the brain section incubated with USPIO-PHO but not with USPIO. The Fe staining colocalized with the core of neuritic plaques (Sirius red staining). 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.

References

1. Wang Y.X., Hussain S.M., Krestin G.P. *Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging.* Eur Radiol. 2001;11(11):2319–31. PubMed PMID: 11702180.
2. Forstl H., Kurz A. *Clinical features of Alzheimer's disease.* Eur Arch Psychiatry Clin Neurosci. 1999;249(6):288–90. PubMed PMID: 10653284.
3. Hardy J. *The relationship between amyloid and tau.* J Mol Neurosci. 2003;20(2):203–6. PubMed PMID: 12794314.
4. Brandt R., Leschik J. *Functional interactions of tau and their relevance for Alzheimer's disease.* Curr Alzheimer Res. 2004;1(4):255–69. PubMed PMID: 15975055.
5. de Leon M.J., DeSanti S., Zinkowski R., Mehta P.D., Pratico D., Segal S., Clark C., Kerkman D., DeBernardis J., Li J., Lair L., Reisberg B., Tsui W., Rusinek H. *MRI and CSF studies in the early diagnosis of Alzheimer's disease.* J Intern Med. 2004;256(3): 205–23. PubMed PMID: 15324364.
6. Nordberg A. *PET imaging of amyloid in Alzheimer's disease.* Lancet Neurol. 2004;3(9): 519–27. PubMed PMID: 15324720.
7. Bacskai B.J., Hickey G.A., Skoch J., Kajdasz S.T., Wang Y., Huang G.F., Mathis C.A., Klunk W.E., Hyman B.T. *Four-dimensional multiphoton imaging of brain entry, amyloid binding, and clearance of an amyloid-beta ligand in transgenic mice.* Proc Natl Acad Sci U S A. 2003;100(21):12462–7. PubMed PMID: 14517353.
8. Wu C., Pike V.W., Wang Y. *Amyloid imaging: from benchtop to bedside.* Curr Top Dev Biol. 2005;70:171–213. PubMed PMID: 16338342.

9. McLachlan S.J., Morris M.R., Lucas M.A., Fisco R.A., Eakins M.N., Fowler D.R., Scheetz R.B., Olukotun A.Y. *Phase I clinical evaluation of a new iron oxide MR contrast agent.* J Magn Reson Imaging. 1994;4(3):301–7. PubMed PMID: 8061425.
10. Weissleder R., Elizondo G., Wittenberg J., Rabito C.A., Bengele H.H., Josephson L. *Ultrasmall superparamagnetic iron oxide: characterization of a new class of contrast agents for MR imaging.* Radiology. 1990;175(2):489–93. PubMed PMID: 2326474.
11. Stillman A.E., Wilke N., Li D., Haacke M., McLachlan S. *Ultrasmall superparamagnetic iron oxide to enhance MRA of the renal and coronary arteries: studies in human patients.* J Comput Assist Tomogr. 1996;20(1):51–5. PubMed PMID: 8576482.
12. Anzai Y., Piccoli C.W., Outwater E.K., Stanford W., Bluemke D.A., Nurenberg P., Saini S., Maravilla K.R., Feldman D.E., Schmiedl U.P., Brunberg J.A., Francis I.R., Harms S.E., Som P.M., Tempany C.M. *Evaluation of neck and body metastases to nodes with ferumoxtran 10-enhanced MR imaging: phase III safety and efficacy study.* Radiology. 2003;228(3):777–88. PubMed PMID: 12954896.
13. Larbanoix, L., C. Burtea, S. Laurent, F. Van Leuven, G. Toubeau, L.V. Elst, and R.N. Muller, *Potential amyloid plaque-specific peptides for the diagnosis of Alzheimer's disease.* Neurobiol Aging, 2008