Gd-DTPA-Bz-poly(α,L-glutamic acid)

GdLPG

Huiming Zhang, PhD[1]

Created: January 9, 2009; Updated: January 26, 2009.

Chemical name:	Gd-DTPA-Bz-poly(α, L-glutamic acid)	
Abbreviated name:	GdLPG	
Synonym:	L-PG-DTPA-Gd, PG-Bz-DTPA-Gd	
Agent category:	Polymer	
Target:	Other	
Target category:	Other – blood pool agent	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal/contrast:	Gadolinium	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is currently available in PubChem.

Background

[PubMed]

Blood pool contrast agents (BPCAs) used in magnetic resonance imaging (MRI) are paramagnetic contrast agents designed to remain in the blood for a prolonged time (1). Macromolecule-based gadolinium (Gd(III)) complexes are excellent candidates for BPCAs in the context of overcoming the limitations of low molecular weight contrast agents, such as the rapid elimination for blood pool, nonspecific extravasation into surrounding tissue, and poor relaxation enhancement efficiency (2). BPCAs can significantly increase the T_1 relaxation rate because of their elongation of rotation correlation time (τ_R) (3), and they can produce persistently enhanced signals in a long acquisition time. In addition to the applications in magnetic resonance angiography, BPCAs are used to target necrotic myocardium (4, 5), to access myocardial viability (6),

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

NLM Citation: Zhang H. Gd-DTPA-Bz-poly(α,L-glutamic acid). 2009 Jan 9 [Updated 2009 Jan 26]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

and to detect various tumors (7, 8). The size of BPCAs controls their extravasation from the leaky vasculatures into the surrounding interstitia *via* the enhanced permeability and retention (EPR) effect (9). This often occurs wherever an inflammatory response is present, such as cancer, arthritis, and vascular diseases (2). On the other hand, the degradation and clearance of BPCAs from the body creates a safety issue; i.e., the tissue retention-induced toxicity of BPCAs is a primarily critical factor for the use of BPCAs in clinics. Thus, the development of biodegradable BPCAs becomes very important (10).

Poly(α,L-glutamic acid) (PG) is an anionic biocompatible macromolecule that has been used for drug delivery in a variety of clinical trials (11). In PG, the naturally occurring L-glutamic acids are linked by amide bonds, which are readily degradable by lysosomal enzymes into its basic unit (L-glutamic acid) in cells. The pendant free γ-carboxyl in each repeating unit of PG provides a functional group for attachment of drugs, therapeutic agents, and/or imaging contrast agents. Gd-Labeled diethylenetriamine pentaacetic acid-Bz-PG (GdLPG) is a PG attached with numerous Gd-DTPAs, which can be used as BPCAs in MRI (12, 13).

Synthesis

[PubMed]

Wen et al. described the detailed synthesis of GdLPG (13). PG (M_n ~42 kDa) was conjugated with p-aminobenzyldiethylenetriamine pentaacetic (acid) tert-butyl ester in the presence of 1,3-diisopropylcarbodiimde as the coupling reagent. The produced PG-BZ-DTPA, in which 50 of 278 glutamic acid units were attached to Bz-DTPA, was reacted with $GdCl_3$ to produce GdLPG, which has a calculated M_w of 77 kDa and contains 12.3% Gd content or 0.22 mol Gd/mol COOH.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The T_1 and T_2 relaxivities of GdLPG were measured at different magnetic fields (12, 13). The T_1 relaxivity was 21 Gd $mM^{-1}s^{-1}$ at 1.5 T and 8.1 Gd $mM^{-1}s^{-1}$ at 4.7 T, whereas the T_2 relaxivity was 27 Gd $mM^{-1}s^{-1}$ at 1.5 T and 21.5 Gd $mM^{-1}s^{-1}$ at 4.7 T.

The degradation of GdLPG in the presence of cathepsin B *in vitro* was evaluated as a function of time (13). GdLPG degraded rapidly, as shown by the complete disappearance of the main polymeric peak within 24 h.

Animal Studies

Rodents

[PubMed]

Wen et al. studied the biodistribution of GdLPG in mice using ^{111}In-labeled GdLPG (13). C3Hf/Kam mice (20–25 g, $n = 4$) bearing MCa-4 tumors ~8 mm in diameter were injected intravenously with ^{111}In-labeled GdLPG (0.4 mg, 15 μCi). Animals were euthanized at 5 min, 2 h, 24 h, and 49 h after injection, and the tissues were harvested for gamma counting. Immediately after injection, GdLPG exhibited a high blood activity of 28.50 ± 1.66% injected dose per gram (% ID/g) at 5 min, which decreased to 7.72 ± 0.28% ID/g at 2 h and appeared to be negligible after 24 h. At 2–48 h the kidney exhibited the highest uptakes: 8.4 ± 0.37% ID/g at 5 min, 20.77 ± 4.70% ID/g at 2 h, 17.54 ± 2.70% ID/g at 24 h, and 10.07 ± 0.61% ID/g at 48 h. The liver exhibited moderate uptake: 5.14 ± 0.29% ID/g at 5 min, 8.3 ± 1.47% ID/g at 2 h, 11.10 ± 1.72% ID/g at 24 h, and 9.36 ± 0.43% ID/g at 48 h. The distribution in the tumor was 0.73 ± 0.14% ID/g at 5 min, 2.42 ± 0.77% ID/g at 2 h, 1.74 ± 0.54% ID/g at 24 h, and 2.27 ± 0.22% ID/g at 48 h. The distribution in the muscle was low at all time points (<1% ID/g).

Wen et al. examined the relaxation enhancement of GdLPG *in vivo* at 1.5 T (13). Mice bearing MCa-4 tumors were intravenously injected with GdLPG at a dose of 0.04 mmol Gd/kg. T_1-Weighted images were collected before injection and at 10 min, 2 h, and 24 h after injection. The blood vessels such as the vena cava as well as myocardial, hepatic, lung, and renal perfusion were clearly visualized at 2 h and returned to the precontrast level at 24 h. However, the contrast in some tumoral regions appeared to be enhanced at 24 h, suggesting an enhanced permeability and retention of GdLPG in solid tumors.

Jackson et al. used GdLPG to examine solid tumors *in vivo* at 4.7 T (12). CD-1 nude mice bearing Colo-205 tumors were injected intravenously with GdLPG at a dose of 0.04 mmol Gd/kg on days 0, 2, 4, and 7. MRI images were collected before injection and 2–4 days after each injection. The images acquired on day 2 (2 days after the first dose), day 4 (2 days after the second dose), day 7 (3 days after the third dose), and day 11 (4 days after the fourth and last dose) all exhibited a similarly enhanced pattern in the tumoral regions. In particular, the central zone of the tumor was significantly enhanced. At the end of the final imaging session, the mice were euthanized and the tumors were excised immediately for histological analysis. A hematoxylin and eosin– (H&E) stained section of the tumor, which was in the same plane as the MRI, showed that the areas of necrosis closely resembled the areas with enhanced MRI signals. This result suggested a significant accumulation of GdLPG in necrotic tissues.

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.

NIH Support

CA90810, CA 16672, EB00174

References

1. Weinmann H.J., Ebert W., Misselwitz B., Schmitt-Willich H. Tissue-specific MR contrast agents. Eur J Radiol. 2003;**46**(1):33–44. PubMed PMID: 12648800.
2. Mohs A.M., Lu Z.R. Gadolinium(III)-based blood-pool contrast agents for magnetic resonance imaging: status and clinical potential. Expert Opin Drug Deliv. 2007;**4**(2): 149–64. PubMed PMID: 17335412.
3. Lauffer R.B. Paramagnetic metal complexes as water proton relaxation agents for NMR imaging:Theory and design. Chem. Rev. 1987;**87**:901–927.
4. Kroft L.J., de Roos A. Blood pool contrast agents for cardiovascular MR imaging. J Magn Reson Imaging. 1999;**10**(3):395–403. PubMed PMID: 10508301.
5. Muhler A. Assessment of myocardial perfusion using contrast-enhanced MR imaging: current status and future developments. Magma. 1995;**3**(1):21–33. PubMed PMID: 7600173.
6. Schmiedl U., Moseley M.E., Sievers R., Ogan M.D., Chew W.M., Engeseth H., Finkbeiner W.E., Lipton M.J., Brasch R.C. Magnetic resonance imaging of myocardial infarction using albumin-(Gd-DTPA), a macromolecular blood-volume contrast agent in a rat model. Invest Radiol. 1987;**22**(9):713–21. PubMed PMID: 3679762.
7. Kiessling F., Morgenstern B., Zhang C. Contrast agents and applications to assess tumor angiogenesis in vivo by magnetic resonance imaging. Curr Med Chem. 2007;**14**(1):77–91. PubMed PMID: 17266569.
8. Daldrup H.E., Roberts T.P., Muhler A., Gossmann A., Roberts H.C., Wendland M., Rosenau W., Brasch R.C. , and , . .Radiologe. 1997;**37**(9):733–40. PubMed PMID: 9424619.
9. Weissleder R., Bogdanov A. Jr, Tung C.H., Weinmann H.J. Size optimization of synthetic graft copolymers for in vivo angiogenesis imaging. Bioconjug Chem. 2001;**12**(2):213–9. PubMed PMID: 11312682.
10. Lu Z.R., Wang X., Parker D.L., Goodrich K.C., Buswell H.R. Poly(l-glutamic acid) Gd(III)-DOTA conjugate with a degradable spacer for magnetic resonance imaging. Bioconjug Chem. 2003;**14**(4):715–9. PubMed PMID: 12862423.
11. Li C. Poly(L-glutamic acid)--anticancer drug conjugates. Adv Drug Deliv Rev. 2002;**54**(5):695–713. PubMed PMID: 12204599.
12. Jackson E.F., Esparza-Coss E., Wen X., Ng C.S., Daniel S.L., Price R.E., Rivera B., Charnsangavej C., Gelovani J.G., Li C. Magnetic resonance imaging of therapy-

induced necrosis using gadolinium-chelated polyglutamic acids. Int J Radiat Oncol Biol Phys. 2007;**68**(3):830–8. PubMed PMID: 17379450.

13. Wen X., Jackson E.F., Price R.E., Kim E.E., Wu Q., Wallace S., Charnsangavej C., Gelovani J.G., Li C. Synthesis and characterization of poly(L-glutamic acid) gadolinium chelate: a new biodegradable MRI contrast agent. Bioconjug Chem. 2004;**15**(6):1408–15. PubMed PMID: 15546209.