^{177}Lu-DOTA-Gly-4-aminobenzoyl-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

[^{177}Lu]-AMBA

Huiming Zhang, PhD[1]

Created: October 1, 2008; Updated: November 17, 2008.

Chemical name:	^{177}Lu-DOTA-Gly-4-aminobenzoyl-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2	
Abbreviated name:	[^{177}Lu]-AMBA	
Synonym:		
Agent category:	Peptide	
Target:	Gastrin-releasing peptide receptor (GRP-R)	
Target category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT)	
Source of signal/contrast:	^{177}Lu	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is currently available in PubChem.

Background

[PubMed]

Bombesin (BBN) is a tetradecapeptide isolated from the European fire-bellied frog (*Bombina bombina*) (1). BBN possesses a specific C-terminus (Gly-His-Leu-Met), which is necessary for its biological activity (2). Several peptides that are structurally related to BBN have been identified in mammals. Gastrin-releasing peptide (GRP) is a peptide of 27 amino acids from porcine gastric tissues with Gly-His-Leu-Met at its C-terminus. Neuromedin B (NMB) is a peptide of 32 amino acids from porcine spinal cords with Gly-

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

NLM Citation: Zhang H. ^{177}Lu-DOTA-Gly-4-aminobenzoyl-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2. 2008 Oct 1 [Updated 2008 Nov 17]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

His-Phe-Met at its C-terminus. These peptides are the ligands of a group of receptors called BBN receptors (BB-R). The mammalian BB-R family consists of three subtypes, including the GRP-preferring receptor (GRP-R or BB_2-R (384 amino acids)), the NMB-preferring receptor (NMB-R or BB_1-R (390 amino acids)), and an orphan receptor (BB_3-R (399 amino acids)) (3). These subtypes of BB-R are overexpressed in various diseased tissues. For example, GRP acts as a neurotransmitter and an endocrine cell-growth factor to regulate various functions of gastrointestinal and central nervous systems and to stimulate cell proliferations in lung, colon, stomach, pancreas, breast, and prostate cancers in humans (4). GRP binds to GRP-R as an agonist and is subsequently transported to the perinuclear space *via* receptor-mediated endocytosis (1), which leads to an accumulation in GRP-R–positive tissues. Thus, tagging GRP with an imaging probe allows for assessment of GRP-R *in vivo*.

^{177}Lu-(4,7,10-Tetraazacyclododecane-*N,N′,N″,N‴*-tetracetic acid (DOTA))-Gly-4-aminobenzoyl-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2 (^{177}Lu-AMBA) is used with single-photon emission computed tomography (SPECT) imaging of GRP-R (5). ^{177}Lu-AMBA consists of two components: a peptide of eight amino acids that is composed of the seven common amino acids in the C-terminus of BBN/GRP (Trp-Ala-Val-Gly-His-Leu-Met) and a complex of ^{177}Lu-DOTA attached to the N-terminus of the peptide *via* a glycyl-4-aminobezoic acid linker. The small peptide accounts for the biological potency and possesses many advantages such as high *in vivo* stability, high uptake in tumors, low uptake in non-target tissues, and a rapid clearance from blood *via* the kidney (3). ^{177}Lu is a radionuclide from the group of rare earth radionuclides, and it is produced by neutron bombardment of purified target material in reactors (6). With a half-life of 6.71 days for β^- emission at 498 keV and 78% branch fraction, ^{177}Lu has been a very promising radionuclide in radiotherapy for effective destruction of small tumors and metastasis (optimal size 1.2–3.0 mm) while sparing normal tissue (7). ^{177}Lu also emits low-energy gamma rays at 208 and 113 keV with 10% and 6% abundance, respectively, which allows for direct monitoring of the activity distribution with SPECT and subsequent dosimetry calculations. ^{177}Lu-AMBA is currently under phase I clinical trials (8).

Synthesis

[PubMed]

Lantry et al. reported the synthesis of ^{177}Lu-AMBA (5). AMBA was produced with solid-phase peptide synthesis at a 14.5% yield followed by reaction with ~2.2 GBq (59.4 mCi) $^{177}LuCl_3$ with specific activity of 103.6-151.3 GBq/μmol (2.8–4.09 Ci/μmol) in 0.05 N HCl for 10 min at 100°C. The produced ^{177}Lu-AMBA was purified with high-performance liquid chromatography (HPLC).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Lantry et al. examined the specificity of *in vitro* ^{177}Lu-AMBA binding to GRP-R in human prostate cancer PC-3 cells (~2.5×10^5 GRP-R per cell) (5). The 50% inhibition concentration (IC_{50}) was measured *via* competition studies in which six cold metalated ligand (^{175}Lu-AMBA) solutions ranging from 1.25×10^{-9} M to 5.0×10^{-8} M were used to inhibit the binding of ^{125}I-[Tyr^4]-BBN with specific activity of 2.2 Ci/μmol (81.4 GBq/μmol). The binding affinity (K_d) and the maximum binding capacity (B_{max}) were measured *via* direct saturation studies, in which 10 ^{177}Lu-AMBA solutions ranging from 0.0-0.37 MBq/ml (0–0.01 Ci/ml) were used. Both the inhibitory and the saturation studies were performed at 4°C to eliminate interference from internalization and degradation. The measured IC_{50}, K_d, and B_{max} values were 2.50 ± 0.50 nmol/L, 1.02 nmol/L, and 414 fmol per 10^6 PC-3 cells, respectively. The internalization of ^{177}Lu-AMBA was evaluated in adherent PC-3 cells at 37°C. After 40 min of incubation, 76.8 ± 1.8% of ^{177}Lu-AMBA was internalized. Only 2.9 ± 1.8% was effluxed in 2 h; most (78%) remained in the form of parent ^{177}Lu-AMBA as found with HPLC. ^{177}Lu-AMBA appeared to be very stable; its half-life time was 38.8 h in human plasma and 3.1 h in mouse plasma. The specificity of ^{177}Lu-AMBA binding to BB-R subtypes was examined with receptor autoradiography *in vitro*. Tissue sections of human ileal carcinoid (NMB-R), human prostate carcinoma (GRP-R), and human bronchial carcinoid (BB_3-R) were used for studies. ^{177}Lu-AMBA bound specifically to GRP-R (IC_{50}, 0.8 nmol) and NMB-R (IC_{50}, 0.9 nmol/L) at high affinities, but less exhibited less preference for BB_3-R (IC_{50} >1,000 nmol).

Animal Studies

Rodents

[PubMed]

Lantry et al. evaluated the biodistribution of ^{177}Lu-AMBA in mice *in vivo* (5). Nude mice (age 4–6 wk, n = 4) bearing PC-3 tumors (~0.5 g) were intravenously injected with ^{177}Lu-AMBA 0.185 MBq/ml with specific activity of 118.4 GBq/μmol (3.2 Ci/μmol). At 1 h or 24 h after injection, mice were euthanized and the tissues were harvested for gamma counting of residual radioactivity. At 1 h, measured radioactivity (percentage of injected dose (% ID)) was found to be 6.35 ± 2.23 in tumor, 0.46 ± 0.20 in blood, 0.25 ± 0.08 in liver, 2.95 ± 0.79 in kidney, 17.78 ± 4.07 in pancreas, 11.22 ± 3.29 in gastrointestine, and 55.66 ± 7.28 in bladder/urine. At 24 h, measured radioactivity was 3.39 ± 0.85 in tumor, 0.03 ± 0.02 in blood, 0.21 ± 0.368 in liver, 0.91 ± 0.25 in kidney, 12.28 ± 3.5 in pancreas, and 5.77 ± 1.79 in gastrointestine; no detectable amount was found in bladder/urine. ^{177}Lu-AMBA was excreted primarily *via* the kidney.

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. Varvarigou A., Bouziotis P., Zikos C., Scopinaro F., De Vincentis G. Gastrin-releasing peptide (GRP) analogues for cancer imaging. Cancer Biother Radiopharm. 2004;**19**(2):219–29. PubMed PMID: 15186603.
2. Ohki-Hamazaki H., Iwabuchi M., Maekawa F. Development and function of bombesin-like peptides and their receptors. Int J Dev Biol. 2005;**49**(2-3):293–300. PubMed PMID: 15906244.
3. Dijkgraaf I., Boerman O.C., Oyen W.J., Corstens F.H., Gotthardt M. Development and application of peptide-based radiopharmaceuticals. Anticancer Agents Med Chem. 2007;**7**(5):543–51. PubMed PMID: 17896914.
4. Smith C.J., Gali H., Sieckman G.L., Hayes D.L., Owen N.K., Mazuru D.G., Volkert W.A., Hoffman T.J. Radiochemical investigations of 177Lu-DOTA-8-Aoc-BBN[7-14]NH2: an in vitro/in vivo assessment of the targeting ability of this new radiopharmaceutical for PC-3 human prostate cancer cells. Nucl Med Biol. 2003;**30**(2):101–9. PubMed PMID: 12623108.
5. Lantry L.E., Cappelletti E., Maddalena M.E., Fox J.S., Feng W., Chen J., Thomas R., Eaton S.M., Bogdan N.J., Arunachalam T., Reubi J.C., Raju N., Metcalfe E.C., Lattuada L., Linder K.E., Swenson R.E., Tweedle M.F., Nunn A.D. 177Lu-AMBA: Synthesis and characterization of a selective 177Lu-labeled GRP-R agonist for systemic radiotherapy of prostate cancer. J Nucl Med. 2006;**47**(7):1144–52. PubMed PMID: 16818949.
6. Schotzig U., Schrader H., Schonfeld E., Gunther E., Klein R. Standardisation and decay data of 177Lu and 188Re. Appl Radiat Isot. 2001;**55**(1):89–96. PubMed PMID: 11339536.
7. Dvorakova Z., Henkelmann R., Lin X., Turler A., Gerstenberg H. Production of 177Lu at the new research reactor FRM-II: Irradiation yield of 176Lu(n,gamma)177Lu. Appl Radiat Isot. 2008;**66**(2):147–51. PubMed PMID: 17900914.
8. Waser B., Eltschinger V., Linder K., Nunn A., Reubi J.C. Selective in vitro targeting of GRP and NMB receptors in human tumours with the new bombesin tracer 177Lu-AMBA. Eur J Nucl Med Mol Imaging. 2007;**34**(1):95–100. PubMed PMID: 16909223.