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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.
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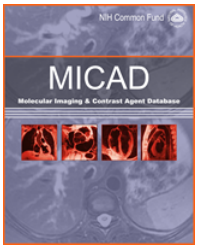

^{177}Lu-DOTA-Gly-4-aminobenzoyl-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

[^{177}Lu]-AMBA

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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-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

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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.

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