^{111}In-DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2

^{111}In-RM2

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Chemical name:	^{111}In-DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2	
Abbreviated name:	^{111}In-RM2	
Synonym:		
Agent category:	Peptide	
Target:	Gastrin-releasing peptide receptor (GRPR)	
Target category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging	
Source of signal\contrast:	^{111}In	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about gastrin-releasing peptide receptor.

Background

[PubMed]

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The amphibian bombesin (BBN or BN, a peptide of 14 amino acids) is an analog of human gastrin-releasing peptide (GRP, a peptide of 27 amino acids) that binds to GRP receptor (GRPR) with high affinity and specificity (1). Both GRP and BBN share an amidated C-terminus sequence homology of seven amino acids, Trp-Ala-Val-Gly-His-Leu-Met-NH_2. BBN-Like peptides have been shown to induce various biological responses in diverse tissues, including the central nervous system (CNS) and the gastrointestinal (GI) system. They also act as potential growth factors for both normal and neoplastic tissues (2). Specific BBN receptors have been identified on CNS and GI tissues, including the pancreas, and on a number of tumor cell lines. The BBN-receptor superfamily includes at least four different subtypes, namely neuromedin B (NMB or BB1), the GRPR subtype (BB2), the BB3 subtype, and the BB4 subtype (3). The findings of GRPR overexpression in various human tumors, such as breast, prostate, lung, colon, ovarian, and pancreatic cancers, provide opportunities for tumor imaging by designing specific molecular imaging agents to target the GRPR.

Currently used targeting GRPR peptides are primarily agonists. Therefore, there is a need for GRPR antagonist radioligands. Llinares et al. (4) developed a series of GRPR peptide antagonists. One of them, D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2 (RM26), has been found to be a selective GRPR antagonist. A DOTA-Gly-benzoyl group was added to the C-terminus to form DOTA-Gly-benzoyl-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2 (RM1). For evaluation as a single-photon emission computed tomography (SPECT) imaging agent for GRPR, ^{111}In has been attached to RM1 to form ^{111}In-RM1 (5). A new GRPR peptide antagonist, DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2 (RM2), has been found to have a higher affinity for GRPR than RM1 and has been labeled with ^{111}In for single-photon emission computed tomography (SPECT) imaging (6).

Related Resource Links:

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

Synthesis

[PubMed]

RM2 was prepared by solid-phase peptide synthesis with >70% yield (6). $^{111}InCl_3$ was added to a solution of RM2 (~6 nmol) in sodium acetate (pH 5). The mixture was heated for 30 min at 95°C. The product, ^{111}In-RM2, was identified with electrospray-mass spectrometry and used without further purification. The labeling yield of ^{111}In-RM2 was >95%, with a specific activity of 30 GBq/μmol (0.81 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Mansi et al. (6) performed *in vitro* inhibition studies of RM1, ^{nat}In-RM1, RM2, and ^{nat}In-RM2 in cultured PC-3 human prostate cells with ^{125}I-BBN; Mansi et al. recorded 50% inhibition concentration (IC_{50}) values of 35.0 ± 13.0, 14.0 ± 3.4 nM, 7.7 ± 3.3, and 9.3 ± 3.3, respectively. ^{111}In-RM1 showed a K_d value (affinity constant) of 8.5 ± 2.7 nM and a B_{max} value (receptor density) of 2.4 ± 0.2 nM, whereas ^{111}In-RM2 showed a higher affinity (K_d, 2.9 ± 0.4 nM) and a lower receptor density (B_{max}, 1.1 ± 0.1 nM). PC-3 cells exhibited a 3.7% uptake of the ^{111}In-RM2 incubation dose at 4 h of incubation at 37°C, with 15.9% of the incubation dose remaining on the cell surface, which indicated a lack of cell internalization of the radioligand. RM2 was able to inhibit the calcium release and receptor internalization induced by BBN indicating antagonist behavior.

Animal Studies

Rodents

[PubMed]

Mansi et al. (6) performed *ex vivo* biodistribution studies of 0.18 MBq (5 μCi) ^{111}In-RM2 in nude mice (n = 4/group) bearing PC-3 tumors. Tumor accumulation values for ^{111}In-RM2 were 15.2 ± 4.8, 11.8 ± 2.4, and 6.8 ± 1.0% injected dose per gram (ID/g) at 1, 4, and 24 h after injection, respectively. ^{111}In-RM2 exhibited a fast blood clearance, with 0.05% ID/g at 4 h after injection. The tumor/blood ratios were 20, 235, and 2,280 at 1, 4, and 24 h after injection, respectively. The initial accumulation was high in the pancreas, kidney, pituitary adrenal, stomach, and intestine at 1 h after injection, with rapid washout by 4 h. Preinjection of excess RM2 peptide (20 nmol, 5 min) inhibited the GRPR-positive tumor, pancreas, stomach, and intestine accumulation by ~90%, with little effect in the other tissues at 4 h after injection.

SPECT imaging in nude mice (n = 2) bearing PC-3 xenografts was performed with 42 MBq (1.1 mCi) ^{111}In-RM2 at 24 after injection. The tumors, kidneys, and urinary bladder were clearly visualized. No blocking studies were reported.

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. Gonzalez N., Moody T.W., Igarashi H., Ito T., Jensen R.T. *Bombesin-related peptides and their receptors: recent advances in their role in physiology and disease states.* Curr Opin Endocrinol Diabetes Obes. 2008;15(1):58–64. PubMed PMID: 18185064.
2. Chung D.H., Evers B.M., Beauchamp R.D., Upp J.R. Jr, Rajaraman S., Townsend C.M. Jr, Thompson J.C. *Bombesin stimulates growth of human gastrinoma.* Surgery. 1992;112(6):1059–65. PubMed PMID: 1455308.
3. Benya R.V., Kusui T., Pradhan T.K., Battey J.F., Jensen R.T. *Expression and characterization of cloned human bombesin receptors.* Mol Pharmacol. 1995;47(1):10–20. PubMed PMID: 7838118.
4. Llinares M., Devin C., Chaloin O., Azay J., Noel-Artis A.M., Bernad N., Fehrentz J.A., Martinez J. *Syntheses and biological activities of potent bombesin receptor antagonists.* J Pept Res. 1999;53(3):275–83. PubMed PMID: 10231715.
5. Mansi R., Wang X., Forrer F., Kneifel S., Tamma M.L., Waser B., Cescato R., Reubi J.C., Maecke H.R. *Evaluation of a 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-conjugated bombesin-based radioantagonist for the labeling with single-photon emission computed tomography, positron emission tomography, and therapeutic radionuclides.* Clin Cancer Res. 2009;15(16):5240–9. PubMed PMID: 19671861.
6. Mansi R., Wang X., Forrer F., Waser B., Cescato R., Graham K., Borkowski S., Reubi J.C., Maecke H.R. *Development of a potent DOTA-conjugated bombesin antagonist for targeting GRPr-positive tumours.* Eur J Nucl Med Mol Imaging. 2011;38(1):97–107. PubMed PMID: 20717822.