^{111}In-Labeled 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid-GSC(succinimidopropionyl-EAYGWNleDF-NH_2)-EAYGWNleDF-NH_2

^{111}In-MGD5

Arvind Chopra, PhD[1]

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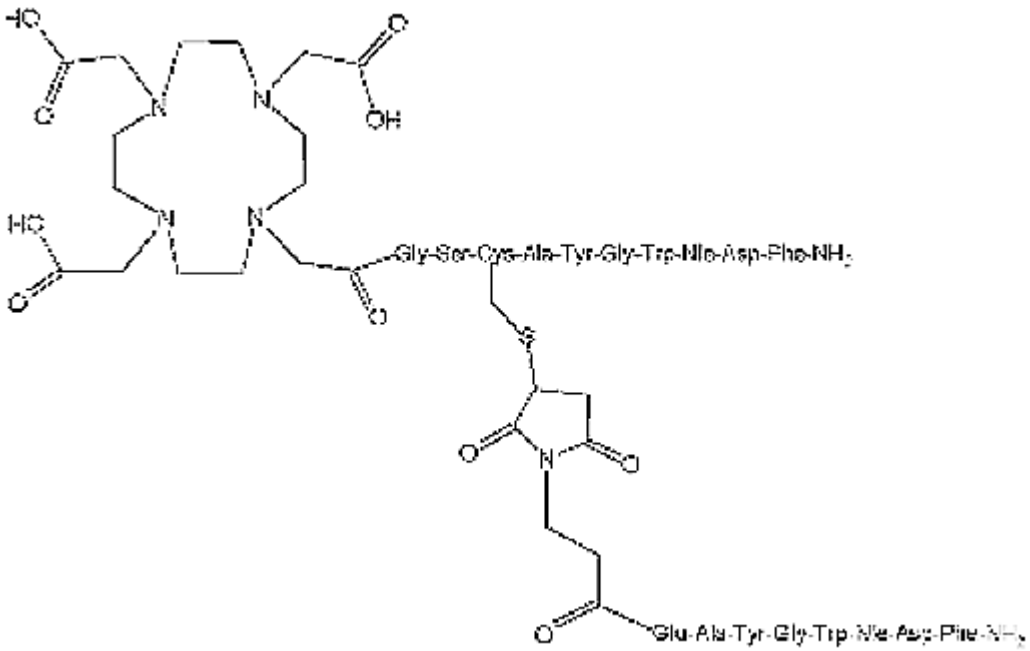
Chemical name:	^{111}In-Labeled 1,4,7,10-tetraazacyclododecane-*N,N',N",N‴*-tetraacetic acid-GSC(succinimidopropionyl-EAYGWNleDF-NH_2)-EAYGWNleDF-NH_2
Abbreviated name:	^{111}In-MGD5
Synonym:	
Agent Category:	Compound
Target:	Gastrin/cholecystokinin subtype 2 receptor (CCK-2R)
Target Category:	Receptor
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{111}In
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of 111In-MGD5.

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Background

[PubMed]

The gastrin/cholecystokinin subtype 2 receptor (CCK-2R) is a G-protein–coupled receptor (for structure, function, and pharmacology of CCK-2R, see Foucaud et al. (1)) that is believed to participate in the development of a variety of cancers and has a characteristic overexpression in the cancerous tumors (2, 3). As a consequence, investigators are interested in exploring the use of CCK-2R ligands, such as gastrin and cholecystokinin (and their derivatives), for the diagnostic imaging and possible therapy of cancers that overexpress this receptor (3-5). Cholecystokinin is the topic of several clinical trials around the world for the treatment of different gastrointestinal disorders and the diagnosis of pancreatic cancer. Several radiolabeled CCK-2R peptides have been evaluated under preclinical (3) and clinical conditions (6) for the visualization of CCK-2R–positive tumors, but the major limitation of using these peptides was reported to be either a high uptake by the kidneys or low accumulation in the tumors or both. During an earlier study, based on the tumor/kidney uptake ratio, an ^{111}In-labeled analog of gastrin (^{111}In-1,4,7,10-tetraazacyclododecane-*N,N',N",N"'*-tetraacetic acid (DOTA)-His-His-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2 (H2-Met or APH070)) was shown to have a low kidney retention, but its uptake by the tumors was low (7). Also, multimerization of small-molecule receptor ligands is known to increase their affinity for the binding site (3), and radiolabeled dimeric and tetrameric cyclic Arg-Gly-Asp peptides have been used successfully to visualize $\alpha_v\beta_3$ integrin receptors (8). On the basis of the observations described above, Sosabowski et al. (3) decided to evaluate a ^{111}In-labeled dimeric form of APH070 (^{111}In-DOTA-GSC(succinimidopropionyl-EAYGWNleDF-NH_2)-EAYGWNleDF-NH_2 (^{111}In-MGD5)) for its *in vitro* characteristics (stability, cellular internalization, and receptor binding), biodistribution, and its use as an imaging agent for tumor visualization in mice bearing AR42J cell tumors (a rat amphicrine pancreatic acinar cell line (9)).

Other sources of information regarding Gastrin/cholecystokinin subtype 2 receptor (CCK-2R)

Chapters on CCK-2R in MICAD.

Information on gastrin/cholecystokinin receptors in OMIM (Online Mendelian Inheritance in Man).

Human gastrin protein and nucleotide sequences.

NLM Citation: Chopra A. ^{111}In-Labeled 1,4,7,10-tetraazacyclododecane-*N,N',N",N'"*-tetraacetic acid-GSC(succinimidopropionyl-EAYGWNleDF-NH_2)-EAYGWNleDF-NH_2. 2010 Jan 8 [Updated 2010 Feb 18]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Information on human cholecystokinin gene.

Synthesis

[PubMed]

The synthesis, purification, and ^{111}In labeling of MGD5 have been described by Sosabowski et al. (3). The radiochemical yield, purity, and specific activity of the labeled compound were not reported. ^{111}In-MGD5 was reported to be stable in mouse plasma at 37°C and remained 95% and ~90% intact at 5 h and 24 h, respectively, after exposure to plasma as determined with high-performance liquid chromatography (HPLC).

^{111}In-APH070 was also synthesized for comparison studies with ^{111}In-MGD5 (3). The radiochemical yield, purity, and specific activity of ^{111}In-APH070 were not reported. The stability of this labeled compound in human blood at 37°C was reported to be 95% at 4 h and 62% at 24 h (compared to 98% in phosphate-buffered saline) as determined with HPLC (7).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Competition receptor binding assays with increasing concentrations of non-radioactive MGD5 or APH070 were performed on AR24J cell membranes with ^{111}In-APH070 as the receptor ligand (3). MGD5 was shown to have a higher affinity for CCK-2R (50% inhibitory concentration (IC_{50}) = 1.04 ± 0.16 nM) compared to an IC_{50} of 5.59 ± 1.46 nM for APH070. Using saturation binding assays with intact AR24J cells, the dissociation constants for ^{111}In-MGD5 and ^{111}In-APH070 were reported to be 0.69 ± 0.14 and 2.9 ± 0.6 nM, respectively (3). These studies indicated that MGD5 is a superior to APH070 as a ligand for CCK-2R.

The internalization rate of ^{111}In-MGD5 by AR2J cells was almost twice that of ^{111}In-APH070 (0.24%/min *versus* 0.14%/min) (3), and at 120 min after exposure to the labeled compounds, 31.1% and 16.7% of ^{111}In-MGD5 and ^{111}In-APH070 were respectively internalized by the cells.

Animal Studies

Rodents

[PubMed]

The biodistribution of ^{111}In-MGD5 was studied in nude mice bearing AR24J cell tumors (n = 3 and 4 animals in two separate studies) and compared to the biodistribution of ^{111}In-APH070 performed with two other groups (n = 4 and 5, respectively) of the same tumor-bearing mice (3). The labeled peptides were injected into the animals through the tail vein, and the mice were euthanized 4 h after injection. Major organs of the animals

were harvested to determine the amount of accumulated radioactivity. The uptake of ^{111}In-MGD5 (~5.5% of injected dose per gram tissue (% ID/g)) by the tumor was significantly higher (6-fold; $P = 0.01$) compared with that of ^{111}APH070 (~0.90% ID/g). The kidney uptake of ^{111}In-MGD5 was also higher (~3% ID/g) than ^{111}In-APH070 (~1.5% ID/g). The tumor/kidney ratios for the two radiochemicals were 1.66 (for ^{111}In-MGD5) and 0.6 (for ^{111}In-APH070), indicating that the dimer was possibly superior to the monomer as an imaging agent. Static imaging (single-photon emission computer tomography/computed tomography (SPECT/CT) of mice (the number of animals used per imaging agent was not reported) respectively injected with the two radiochemicals confirmed the results obtained during the biodistribution investigation (3).

When the mice were co-injected with ^{111}In-MGD5 in presence of excess (100 μg/animal) non-radioactive MGD5, the tumors were reported to show a 10-fold reduction in accumulation of the label, and the investigators concluded that uptake of the radiochemical was specific to the tumor (3).

Results obtained after SPECT/CT imaging of mice injected with either ^{111}In-MGD5 (n = 1 animal) or ^{111}In-APH070 (n = 1 animal) showed that accumulation of radioactivity in various organs of the mice was similar to that observed during the biodistribution studies (3). Dynamic SPECT imaging of the animals showed that there was a rapid uptake of both labeled compounds by the various organs and the tumors during the initial 5 min after the injection, followed by a gradual washout of radioactivity from the various tissues, including tumors. The clearance of ^{111}In-APH070 from the different tissues was reported to be faster than that of ^{111}In-MGD5. By 2 h after the injection, 89% of the labeled monomer had washed out from the tissues compared to 58% for the labeled dimer.

From these studies, the investigators concluded that ^{111}In-MGD5 was a suitable ligand to target CCK-2R–overexpressing tumors in animals, but further evaluation in clinical trials is necessary before it can be used in humans (3).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No supplemental information is currently available.

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