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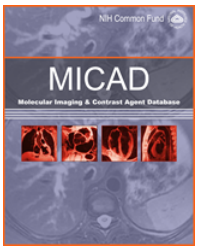

^{68}Ga-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid-p-Cl-Phe-cyclo(D-Cys-Tyr-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)D-Tyr-NH_2

^{68}Ga-DOTA-LM3

Kam Leung, PhD[1]

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Chemical name:	^{68}Ga-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid-p-Cl-Phe-cyclo(D-Cys-Tyr-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)D-Tyr-NH_2	
Abbreviated name:	^{68}Ga-DOTA-LM3	
Synonym:		
Agent category:	Peptide	
Target:	Somatostatin receptor 2 (SSTR2)	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{68}Ga	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about somatostatin.

Background

[PubMed]

Somatostatin (SSTR) is an inhibitor of the release of somatotropin, glucagon, insulin, gastrointestinal hormones, and other secretory proteins (1). SSTR is also known as somatotropin release-inhibiting factor (SRIF). SSTR is a cyclic polypeptide with two biologically active isoforms, SRIF-14 and SRIF-28, of 14 and 28 amino acids, respectively. SRIF has a short plasma half-life of <3 min (2). SSTR receptors (SSTRs) (G-protein–coupled) have been found on a variety of neuroendocrine tumors and cells of the immune system, and five individual subtypes (SSTR1–SSTR5) have been identified and subsequently cloned from animal and human tissues (3, 4). SST also inhibits cell proliferation and promotes apoptosis through binding to specific cell-surface SSTRs (5).

Author Affiliation: 1 National for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

^{111}In-Diethylenetriamine pentaacetic acid-octreotide (^{111}In-DTPA-OCT) is an SST analog that, over the last decade, has remained the most widely used radiopharmaceutical and the only FDA approved radiotracer for the scintigraphic detection and staging of primary and metastatic neuroendocrine tumors bearing SSTRs with single-photon emission computed tomography (SPECT) (6). It has also shown promising results in peptide-receptor radionuclide therapy (7). Octreotide (OCT) is a cyclic peptide with eight amino acids. ^{111}In-DTPA-OCT binds with high affinity to SSTR2 and SSTR5 and to SSTR3 to a lesser degree, but it does not bind to SSTR1 and SSTR4 (8). A large number of radiolabeled SST analogs have been reported using different radionuclides and different linkers. Currently used targeting SSTR peptides mainly are SSTR2 agonists. Therefore, there is a need for SSTR2 antagonist radioligands (9). p-Cl-Phe-cyclo(D-Cys-Tyr-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)D-Tyr-NH_2 (LM3) is a novel selective SSTR2 antagonist. Fani et al. (10) prepared ^{68}Ga-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid-LM3 (^{68}Ga-DOTA-LM3) as a positron emission tomography (PET) imaging agent for SSTR2.

Related Resource Links:

- Chapters in MICAD (Somatostatin)
- Gene information in NCBI (Somatostatin, SSTR2)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Somatostain, SSTR2)
- Clinical trials (Somatostatin receptor)

Synthesis

[PubMed]

DOTA-LM3 was synthesized *via* standard solid-phase peptide synthesis with a calculated mass of 1,522.0 Da in agreement with mass spectrometry (10). DOTA was incorporated at the N-terminus of the peptide. DOTA-LM3 was purified with high-performance liquid chromatography. ^{68}Ga was complexed to DOTA-LM3 by reaction of DOTA-LM3 with ^{64}Ga in sodium acetate (pH 4.0) for 8 min at 95°C. ^{68}Ga-DOTA-LM3 had a >95% radiochemical purity and specific activity of 100 MBq/nmol (2.7 mCi/nmol) with a labeling yield >95%. ^{68}Ga-DOTA-LM3 had a log D value of -2.13 ± 0.01 and a net charge of +1.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Fani et al. (10) reported that ^{nat}Ga-DOTA-LM3 had 50% inhibition concentration (IC_{50}) values of >1,000, 12.5 ± 4.3, >1,000, >1,000, and >1,000 nM for human SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5 receptors in competition with ^{125}I-SRIF-28, respectively. Immunofluorescence studies showed that [Tyr^3]octreotide (10 nM) triggers receptor internalization whereas ^{nat}Ga-NODAGA-LM3 at a much higher concentration (1,000 nM) does not stimulate receptor internalization in HEK-sst2 cells. ^{nat}Ga-DOTA-LM3 was able to inhibit receptor internalization induced by [Tyr^3]octreotide.

Animal Studies

Rodents

[PubMed]

Fani et al. (10) performed *ex vivo* biodistribution studies with 13.0 MBq (0.35 mCi) ^{68}Ga-DOTA-LM3 in nude mice (n = 3) bearing HEK-sst2 xenografts of at 1 h after injection. The accumulation of radioactivity in the SSTR2 tumor was 28.72 ± 5.58% injected dose per gram (% ID/g). The kidney was the organ that had the highest accumulation (32.50% ID/g), followed by the lung (1.73% ID/g), bone (1.63% ID/g), stomach (1.08% ID/g),

adrenal (1.06% ID/g), pancreas (0.91% ID/g), and liver (0.84% ID/g). Accumulation of radioactivity in the other tissues was low. The concentration in the blood was 1.21% ID/g. The tumor/blood, tumor/liver, tumor/kidney, and tumor/muscle ratios were 24.2, 34.3, 0.9, and 90.6, respectively. As a comparison, ^{68}Ga-DOTA-LM3 accumulation in the kidney was 1-fold higher than ^{64}Cu-NODAGA-LM3 at 1 h after injection with lower tumor/blood, tumor/kidney, and tumor/muscle ratios. Whole-body PET imaging visualized the SSTR2 tumor at 1 h after injection of 6 MBq (0.16 mCi) ^{68}Ga-DOTA-LM3. The visualization was abrogated by co-injection of excess unlabeled peptide.

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. Weckbecker G., Lewis I., Albert R., Schmid H.A., Hoyer D., Bruns C. *Opportunities in somatostatin research: biological, chemical and therapeutic aspects.* . Nat Rev Drug Discov. 2003;2(12):999–1017. PubMed PMID: 14654798.
2. Patel Y.C., Wheatley T. *In vivo and in vitro plasma disappearance and metabolism of somatostatin-28 and somatostatin-14 in the rat.* . Endocrinology. 1983;112(1):220–5. PubMed PMID: 6128222.
3. Corleto V.D., Nasoni S., Panzuto F., Cassetta S., Delle Fave G. *Somatostatin receptor subtypes: basic pharmacology and tissue distribution.* . Dig Liver Dis. 2004;36 Suppl 1:S8–16. PubMed PMID: 15077906.
4. Moller L.N., Stidsen C.E., Hartmann B., Holst J.J. *Somatostatin receptors.* . Biochim Biophys Acta. 2003;1616(1):1–84. PubMed PMID: 14507421.
5. Barnett P. *Somatostatin and somatostatin receptor physiology.* . Endocrine. 2003;20(3):255–64. PubMed PMID: 12721505.
6. Krenning E.P., Kwekkeboom D.J., Bakker W.H., Breeman W.A., Kooij P.P., Oei H.Y., van Hagen M., Postema P.T., de Jong M., Reubi J.C.et al. *Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients.* . Eur J Nucl Med. 1993;20(8):716–31. PubMed PMID: 8404961.
7. Kwekkeboom D.J., Mueller-Brand J., Paganelli G., Anthony L.B., Pauwels S., Kvols L.K. M. O'Dorisio T, R. Valkema, L. Bodei, M. Chinol, H.R. Maecke, and E.P. Krenning, *Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs.* J Nucl Med. 2005;46 Suppl 1:62S–6S. PubMed PMID: 15653653.
8. Storch D., Behe M., Walter M.A., Chen J., Powell P., Mikolajczak R., Macke H.R. *Evaluation of [99mTc/EDDA/HYNIC0]octreotide derivatives compared with [111In-DOTA0,Tyr3, Thr8]octreotide and [111In-DTPA0]octreotide: does tumor or pancreas uptake correlate with the rate of internalization?* . J Nucl Med. 2005;46(9):1561–9. PubMed PMID: 16157541.

9. Reubi J.C., Schar J.C., Waser B., Wenger S., Heppeler A., Schmitt J.S., Macke H.R. *Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use.* . Eur J Nucl Med. 2000;27(3):273–82. PubMed PMID: 10774879.
10. Fani M., Del Pozzo L., Abiraj K., Mansi R., Tamma M.L., Cescato R., Waser B., Weber W.A., Reubi J.C., Maecke H.R. *PET of somatostatin receptor-positive tumors using 64Cu- and 68Ga-somatostatin antagonists: the chelate makes the difference.* . J Nucl Med. 2011;52(7):1110–8. PubMed PMID: 21680701.