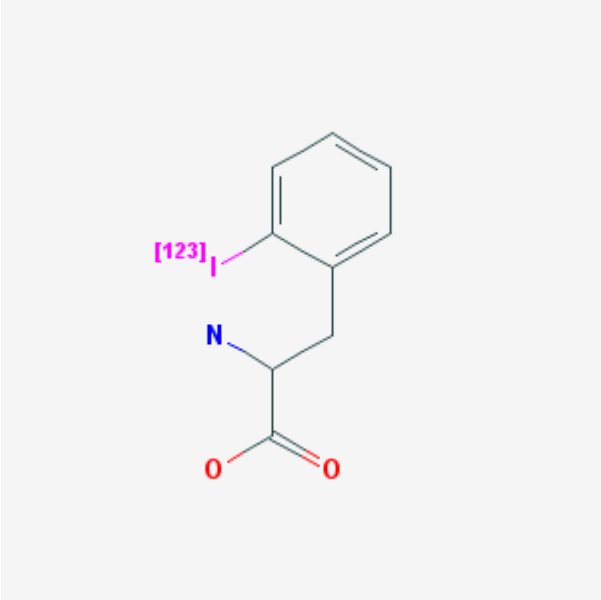
[^{123}I]-2-Iodo-2-amino-3-phenylpropanoic acid

2-[^{123}I]I-L-PA

Arvind Chopra, PhD[1]

Created: June 3, 2008; Updated: July 3, 2008.

Chemical name:	[^{123}I]-2-Iodo-2-amino-3-phenylpropanoic acid
Abbreviated name:	2-[^{123}I] I-L-PA
Synonym:	2-[^{123}I]-iodo-L-phenylalanine
Agent Category:	Compound
Target:	Tumors
Target Category:	Transport through L-type amino acid transporter
Method of detection:	Single-photon emission computed tomography (SPECT); planar gamma imaging
Source of Signal/ Contrast:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans



Click on the above structure of 2-[^{123}I]-iodo-L-phenylalanine for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

Background

[PubMed]

Although [^{18}F]fluoro-deoxyglucose ([^{18}F]FDG) is often used for the detection of malignant tumors, it has limitations because the radiochemical is also nonselectively taken up by inflamed or infected tissue (1-3). Compared with [^{18}F]FDG, labeled amino acids (aa) such as ^{11}C-methionine, ^{18}F-tyrosine, and their derivatives have been shown to be superior at distinguishing tumors from infection or inflammation in humans because these radiochemicals are taken up by the cells through a specialized transport system that has an upregulated expression in proliferating cells (4). The upregulation was observed primarily in cells of the tumor tissue, and normal tissue shows little change in expression of the aa transporters (because the cells divide slowly and only when necessary). This phenomenon is believed to be necessary for tumor cell survival because it supports the increased aa demand for protein synthesis in the rapidly dividing cells (5). One of the transporters, described as the major vehicle of large, neutral aa such as phenylalanine, leucine, and tyrosine, is known as the L system (L-type aa transporter 1; LAT1) and is independent of sodium for the transport of these aa (5). Different compounds, including aa, labeled with radioactive fluorine (^{18}F) or carbon (^{11}C) have been used to study tumors and to predict survival after radiotherapy with positron emission tomography (PET) (6-8). However, PET is not widely available, and investigators have developed aa probes that can be used with single-photon emission computed tomography (SPECT) to study tumors because this method is more available than PET (9).

Labeled with radioactive iodine (as ^{123}I or ^{125}I), aa derivatives such as 2-iodo-L-tyrosine, 4-iodo-L-phenylalanine, and 2-iodo-L-phenylalanine (2I-L-PA) were developed and observed to accumulate in rhabdomyosarcoma (R1M) tumor cells without incorporation into proteins. These derivatives could be used with SPECT to detect malignant tissue (10-12). Several studies, including *in vitro* studies, that used 2-[^{123}I]I-L-PA to investigate the detection of tumors and biodistribution in rats, mice, dogs, and humans are available (13-17).

Synthesis

[PubMed]

The synthesis and labeling of 2I-L-PA with ^{123}I was described by Kersemans et al. (12). A Cu^{1+} non-isotopic exchange method was used to synthesize 2I-L-PA as described elsewhere (18). Briefly, 2-bromo-L-phenylalanine was mixed with copper sulphate

NLM Citation: Chopra A. [^{123}I]-2-Iodo-2-amino-3-phenylpropanoic acid. 2008 Jun 3 [Updated 2008 Jul 3]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

($CuSO_4$), tin sulphate ($SnSO_4$), gentisic acid, and sodium iodide. The solution was flushed with nitrogen gas for 10 min and heated at 160°C for 16 h in a nitrogen atmosphere. The solution was centrifuged, and the products were transferred to a new flask to evaporate all the water. The contents were then purified with high-performance liquid chromatography (HPLC) on a Hibar Lichrosorb RP-select column, and further purification of the product was achieved by repeated dissolving in methanol coupled with evaporation of the solvent. Identification and quality control of the product was performed with nuclear magnetic resonance imaging, liquid chromatography mass spectroscopy, thin-layer chromatography, and HPLC. Chiral chromatography showed that there was no chiral modification to 2-iodo-D-phenylalanine. The yield of this reaction was reported to be 65% (12).

Radioiodination with ^{123}I or ^{125}I was performed as described by Kersemans et al. under acidic and reducing conditions (12). ^{123}I or ^{125}I was mixed with 2I-L-PA in the presence of $CuSO_4$, $SnSO_4$, gentisic acid, and citric acid; the solution was heated at 100°C for 60 min. The reaction was terminated with trisodium citrate dehydrate to obtain an isotonic solution with a pH of at least 4.0. The reaction mixture was then filtered through a silver filter (0.22 μm thick) to sterilize the product and to remove all the free $^{123/125}$I. HPLC on a Sep-Pak C18 column was used to identify the product and control the quality. Chiral chromatography was performed to confirm the absence of any 2-iodo-D-phenylalanine. The radiochemical yield of the iodinations was not reported; the radiochemical purity was >99% with specific activity of 65 GBq/mmol (1.75 Ci/mmol) for the ^{123}I and 11 GBq/mmol (0.297 Ci/mmol) for the ^{125}I labeling. The *in vivo* stability of the halogenated compound ([^{125}I]2I-L-PA) was reported to be 92.7% (7.3% of the radiochemical was dehaloginated) as determined by HPLC. No other degradation products were detected. Ethylendiamine tetraacetic acid did not change dehalogination of the radiotracers (12).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* uptake of [^{125}I]2I-L-PA was studied in R1M rat rabdomyosarcoma cells in the presence or absence of Na^+ ions in MEM buffer (14). The uptake of [^{125}I]2I-L-PA was observed to be a reversible, pseudo–first-order reaction in presence or absence of Na^+ ions, and the radiochemical was not incorporated into the cell proteins. Uptake was shown to occur with the same affinity as L-phenylalanine through a saturable transport system that was inhibited competitively by 2-amino-2-norbornane-carboxylic acid, which selectively uses the L transport system. The transport system used by [^{125}I]2I-L-PA was shown to be of the LAT1 type (14).

The *in vitro* uptake of [^{125}I]2I-L-PA was also studied in R1M cells irradiated with cobalt (^{60}Co) gamma rays and non-irradiated (control) R1M cells (9). Uptake was reported to be higher in cells that survived the radiation treatment than in cells that were not irradiated.

Animal Studies

Rodents

[PubMed]

The uptake of 2-[$^{123/125}$I]I-L-PA was studied with dynamic planar imaging (DPI) in athymic mice bearing R1M cell tumors and NMRI mice with acute inflammation (12). The displacement of 2-[^{123}I]I-L-PA by L-phenylalanine, L-methionine, and L-cysteine in these animals was also investigated. Magnetic resonance imaging was used to visualize the tumors in DPI. For comparison, the uptake of [^{18}F]FDG was compared with the uptake of 2-[^{125}I]I-L-PA in inflamed muscles of the mice. A high, fast, and reversible tumor uptake of 2-[$^{123/125}$I]I-L-PA was reported with a tumorbackground ratio of 6.7 at 60 min. The radiolabeled aa was displaced by L-phenylalanine, L-methionine, or L-cysteine, which indicates that the aa used a reversible LAT transport system. The label was cleared rapidly through the kidneys, and a low accumulation of the tracer was observed in the abdomen and the brain. Compared with [^{18}F]FDG, only a small amount of 2-[^{125}I]I-L-PA was observed in inflamed tissue (inflammation/background ratio of 11.1 ± 1.7 Vs 1.3 ± 0.02, respectively) (12).

With the use of DPI and dissection, Kersemans et al. compared the biodistribution of 2-[^{123}I]I-L-PA with that of 2-[^{123}I]-iodo-L-tyrosine in athymic mice bearing rhabdomyosarcoma tumors (13). Competition studies with L-phenylalanine were also performed to confirm specificity of the tumor uptake. The biodistribution of 2-[^{123}I]I-L-PA and 2-[^{123}I]-iodo-L-tyrosine was also compared with that of [^{18}F]FDG in these animals. No significant difference was observed between the tumor uptake values of 2-[^{123}I]I-L-PA or 2-[^{123}I]-iodo-L-tyrosine, and both tracers were reported to show a rapid, high, and specific accumulation in the tumors. Among the two radiochemicals, 2-[^{123}I] I-L-PA showed a faster clearance from blood through the kidneys. Compared with the slight accumulation of 2-[^{123}I] -iodo-L-tyrosine in the liver, there was no retention of 2-[^{123}I] I-L-PA in this organ. Both 2-[^{123}I]I-L-PA and 2-[^{123}I]-iodo-L-tyrosine appeared to be superior to [^{18}F]FDG for the detection of tumors in the brain and heart because these radiochemicals showed lower accumulation in these organs (see Table 4 in Kersemans et al. (13) for comparison).

In another study, the methods of sedation and data acquisition for 2-[^{123}I]I-L-PA were shown to influence the uptake and biodistribution of this tracer in the various organs in athymic mice bearing R1M tumors (19). Mice treated with phenobarbital and untreated mice were injected with 2-[^{123}I]I-L-PA, and an analysis of variance, *t* test, and clustered boxplot analysis were used to compare the results between the treated and untreated animals. Pentobarbital was reported to reduce the blood clearance and distribution of 2-[^{123}I]I-L-PA toward the peripheral tissue of the animals. These factors were shown to influence the tumor/background ratios as well as nuclear imaging when the animals were treated with phenobarbital. The investigators recommended that the quantitative influence of sedation and the data acquisition methods should be investigated and taken

into consideration for interpretation of the results in animal experiments with 2-[^{123}I]I-L-PA (19).

Bauwens et al. used dynamic and static gamma planar imaging to compare the biodistribution, tumor uptake, and retention of D- and L-2-[^{123}I]I-PA to D- and L-2-[^{123}I]I-tyrosine in Wag/Rij rats bearing R1M tumors (17). The differential uptake ratios of D- and L-2-[^{123}I]I-PA to D- and L-2 -[^{123}I]I-tyrosine were reported to be 2.1, 2.3, 2.5, and 1.7, respectively, and they reached a maximum between 10 and 30 min after the injection. Both D- and L-2-[^{123}I] I-PA showed an almost equal retention in the tumors for up to 48 h that was higher than either D- and L-2-[^{123}I] I-tyrosine (17).

Other Non-Primate Mammals

[PubMed]

Using gamma planar imaging, Peremans et al. investigated the uptake of 2-[^{123}I]I-L-PA in two dogs with synovial cell carcinoma of the tarsus (15). The tracer was observed to accumulate in the tumors (0.8% of the total injected activity) with a tumor/background contrast of 1.85 ± 0.52 at 10 min after administration in one dog; the ratio was 1.84 in the second animal. No metastases were detected with this tracer, which was cleared primarily through the kidneys in these animals.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

Bauwens et al. investigated the biodistribution and dosimetry of D and L isomers of 2-[^{123}I]I-PA in five healthy human volunteers (16). For intra-individual comparison, the subjects received both the D and L isomers of 2-[^{123}II-PA with a 1-week interval between the treatments. Blood and urine samples were collected after the treatment, and whole-body imaging was performed for up to 24 h after administration of the tracers. Both radiochemicals showed a moderate uptake in the heart and liver; with the most accumulation found in the muscle tissue. Clearance for both isomers was through the urinary system, and the bladder wall received/absorbed the highest dose. The effective radiation doses for the D and L isomers were determined to be 0.0106 ± 0.0038 mSv × Bq^{-1} and 0.0120 ± 0.0020 mSv × Bq^{-1}, respectively. Between the two enantomers, 2-[^{123}I]I-D-PA was reported to have a faster clearance, which resulted in a lower dose and reduced background in the subjects.

Supplemental Information

[Disclaimers]

References

1. Bleeker-Rovers C.P., Vos F.J., Corstens F.H., Oyen W.J. Imaging of infectious diseases using [18F] fluorodeoxyglucose PET. Q J Nucl Med Mol Imaging. 2008;**52**(1):17–29. PubMed PMID: 17657204.
2. Rudd J.H., Myers K.S., Bansilal S., Machac J., Pinto C.A., Tong C., Rafique A., Hargeaves R., Farkouh M., Fuster V., Fayad Z.A. Atherosclerosis Inflammation Imaging with 18F-FDG PET: Carotid, Iliac, and Femoral Uptake Reproducibility, Quantification Methods, and Recommendations. J Nucl Med. 2008;**49**(6):871–878. PubMed PMID: 18483100.
3. Ueda S., Tsuda H., Asakawa H., Shigekawa T., Fukatsu K., Kondo N., Yamamoto M., Hama Y., Tamura K., Ishida J., Abe Y., Mochizuki H. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. Jpn J Clin Oncol. 2008;**38**(4):250–8. PubMed PMID: 18407934.
4. Groves A.M., Win T., Haim S.B., Ell P.J. Non-[18F]FDG PET in clinical oncology. Lancet Oncol. 2007;**8**(9):822–30. PubMed PMID: 17765191.
5. Yanagida O., Kanai Y., Chairoungdua A., Kim D.K., Segawa H., Nii T., Cha S.H., Matsuo H., Fukushima J., Fukasawa Y., Tani Y., Taketani Y., Uchino H., Kim J.Y., Inatomi J., Okayasu I., Miyamoto K., Takeda E., Goya T., Endou H. Human L-type amino acid transporter 1 (LAT1): characterization of function and expression in tumor cell lines. Biochim Biophys Acta. 2001;**1514**(2):291–302. PubMed PMID: 11557028.
6. de Boer J.R., Pruim J., Albers F.W., Burlage F., Vaalburg W., van der Laan B.F. Prediction of survival and therapy outcome with 11C-tyrosine PET in patients with laryngeal carcinoma. J Nucl Med. 2004;**45**(12):2052–7. PubMed PMID: 15585481.
7. Ishimori T., Saga T., Nagata Y., Nakamoto Y., Higashi T., Mamede M., Mukai T., Negoro Y., Aoki T., Hiraoka M., Konishi J. 18F-FDG and 11C-methionine PET for evaluation of treatment response of lung cancer after stereotactic radiotherapy. Ann Nucl Med. 2004;**18**(8):669–74. PubMed PMID: 15682847.
8. Sugiyama M., Sakahara H., Sato K., Harada N., Fukumoto D., Kakiuchi T., Hirano T., Kohno E., Tsukada H. Evaluation of 3'-deoxy-3'-18F-fluorothymidine for monitoring tumor response to radiotherapy and photodynamic therapy in mice. J Nucl Med. 2004;**45**(10):1754–8. PubMed PMID: 15471845.
9. Kersemans V., Vergote V., de Gelder V., Madani I., Thierens H., De Neve W., Mertens J., Slegers G., Burvenich C., Peremans K., De Spiegeleer B. The use of [123I]-2-iodo-L-phenylalanine as an early radiotherapy evaluation tool: in vitro R1M Rabdomyosarcoma cell and in vivo mouse experiments. Cancer Biother Radiopharm. 2008;**23**(2):192–201. PubMed PMID: 18454688.

10. Samnick S., Schaefer A., Siebert S., Richter S., Vollmar B., Kirsch C.M. Preparation and investigation of tumor affinity, uptake kinetic and transport mechanism of iodine-123-labelled amino acid derivatives in human pancreatic carcinoma and glioblastoma cells. Nucl Med Biol. 2001;**28**(1):13–23. PubMed PMID: 11182560.
11. Kersemans V., Cornelissen B., Bacher K., Kersemans K., Thierens H., Dierckx R.A., De Spiegeleer B., Slegers G., Mertens J. In vivo evaluation and dosimetry of 123I-2-iodo-D-phenylalanine, a new potential tumor-specific tracer for SPECT, in an R1M rhabdomyosarcoma athymic mouse model. J Nucl Med. 2005;**46**(12):2104–11. PubMed PMID: 16330577.
12. Kersemans V., Cornelissen B., Kersemans K., Bauwens M., Achten E., Dierckx R.A., Mertens J., Slegers G. In vivo characterization of 123/125I-2-iodo-L-phenylalanine in an R1M rhabdomyosarcoma athymic mouse model as a potential tumor tracer for SPECT. J Nucl Med. 2005;**46**(3):532–9. PubMed PMID: 15750170.
13. Kersemans V., Cornelissen B., Kersemans K., Dierckx R.A., De Spiegeleer B., Mertens J., Slegers G. Comparative biodistribution study of the new tumor tracer [123I]-2-iodo-L-phenylalanine with [123I]-2-iodo-L-tyrosine. Nucl Med Biol. 2006;**33**(1):111–7. PubMed PMID: 16459266.
14. Mertens J., Kersemans V., Bauwens M., Joos C., Lahoutte T., Bossuyt A., Slegers G. Synthesis, radiosynthesis, and in vitro characterization of [125I]-2- iodo-L-phenylalanine in a R1M rhabdomyosarcoma cell model as a new potential tumor tracer for SPECT. Nucl Med Biol. 2004;**31**(6):739–46. PubMed PMID: 15246364.
15. Peremans K., Kersemans V., Liuti T., Vandermeulen E., Cornelissen B., Gielen I., De Spiegeleer B., Mertens J., Burvenich C., Slegers G. Use of [123I]-2-iodo-L-phenylalanine as a tumor imaging agent in two dogs with synovial cell sarcoma. Vet Radiol Ultrasound. 2007;**48**(5):471–4. PubMed PMID: 17899985.
16. Bauwens M., Keyaerts M., Lahoutte T., Kersemans K., Caveliers V., Bossuyt A., Mertens J. Intra-individual comparison of the human biodistribution and dosimetry of the D and L isomers of 2-[123I]iodo-phenylalanine. Nucl Med Commun. 2007;**28**(10):823–8. PubMed PMID: 17728613.
17. Bauwens M., Lahoutte T., Kersemans K., Caveliers V., Bossuyt A., Mertens J. D- and L-[123I]-2-I-phenylalanine show a long tumour retention compared with D- and L-[123I]-2-I-tyrosine in R1M rhabdomyosarcoma tumour-bearing Wag/Rij rats. Contrast Media Mol Imaging. 2007;**2**(4):172–7. PubMed PMID: 17683118.
18. Yu J., Zolle I., Mertens J., Rakias F. Synthesis of 2-[131I]iodophenyl-metyrapone using Cu(I)-assisted nucleophilic exchange labelling: study of the reaction conditions. Nucl Med Biol. 1995;**22**(2):257–62. PubMed PMID: 7767321.
19. Kersemans V., De Spiegeleer B., Mertens J., Slegers G. Influence of sedation and data acquisition method on tracer uptake in animal models: [123I]-2-iodo-L-phenylalanine in pentobarbital-sedated tumor-bearing athymic mice. Nucl Med Biol. 2006;**33**(1):119–23. PubMed PMID: 16459267.