L-[*methyl*-^{11}C]Methionine

[^{11}C]MET

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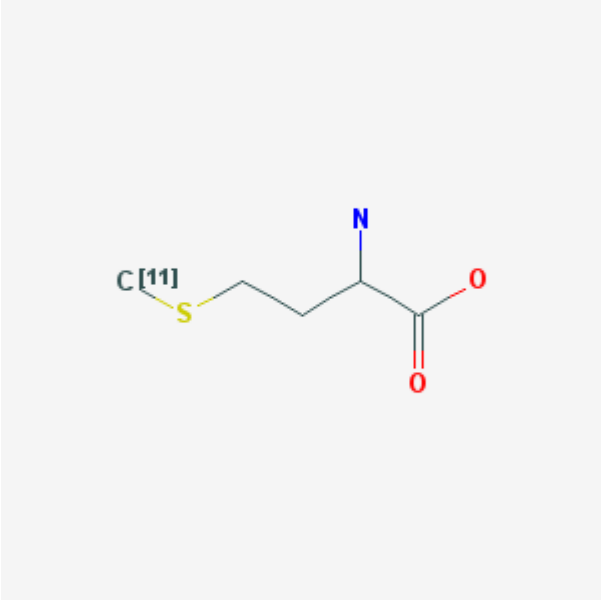
Created: September 15, 2005; Updated: December 21, 2011.

Chemical name:	L-[*methyl*-^{11}C]Methionine
Abbreviated name:	[^{11}C]MET
Synonym:	2-Amino-4-[^{11}C]methylsulfanyl-butanoic acid, l-[*S*-*methyl*^{11}C]methionine
Agent category:	Amino acid
Target:	L-type amino acid transporter system and Na^+-dependent system B^0
Target category:	Neutral amino acid uptake and protein synthesis
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

A variety of [^{11}C] and [^{18}F] labeled amino acids have been studied for potential use in positron emission tomography (PET) oncology (1, 2). Most brain tumors show an increased uptake of amino acids as compared with normal brain (3). These amino acids are composed of naturally occurring amino acids such as, L-[^{11}C]leucine, L-[^{11}C]methionine (MET), and L-[^{11}C]tyrosine and non-natural amino acids such as [^{11}C]aminoisobutyric acid, [^{11}C]1-aminocyclopentane-1-carboxylic acid, and [^{11}C]1-aminocyclobutane-1-carboxylic acid. There are also ^{123}I-labeled amino acids used in imaging in oncology (1, 4, 5).

Some 20 amino acid transporter systems have been identified (1). Most of the amino acids are taken up by tumor cells through an energy-independent L-type amino acid transporter system and a sodium-dependent transporter system A but also a Na^+-dependent system B^0 (6). They are retained in tumor cells due to their higher metabolic activities including incorporation into proteins than most normal cells (1). Malignant transformation increases the use of amino acids for energy, protein synthesis and cell division. Tumor cells were found to have over-expressed transporter systems (7). L-[^{11}C]MET, [^{18}F]fluorotyrosine, L-[^{11}C]leucine, and [^{18}F]fluoro-α-methyl tyrosine have been widely used in detection of tumors (2, 6) but are not approved by the United States Food and Drug Administration. They are moved into cells by various amino acid transporters and are incorporated into proteins. The fraction of radiolabeled amino acid that is incorporated into protein is usually small compared to the total amount taken up into the cell. These natural amino acid images are based on amino acid transport and protein incorporation.

[^{11}C]MET has been widely used in detection of brain, head and neck, lung, and breast cancer as well as lymphomas [PubMed]. It can cross the blood-brain barrier. It is incorporated mainly into proteins but also into lipid, RNA, and DNA. [^{11}C]MET PET imaging is more sensitive to radiotherapy compared to FDG and is useful for monitoring treatment of cancer.

Related Resource Links:

- Chapters in MICAD (Amino acid transporters)
- Gene information in NCBI (L-type amino acid transporter, A-type amino acid transporter)

NLM Citation: Leung K. L-[*methyl*-^{11}C]Methionine. 2005 Sep 15 [Updated 2011 Dec 21]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

- Articles in Online Mendelian Inheritance in Man (OMIM) (Amino acid transporters)
- Clinical trials (Amino acid transporters, L-[^{11}C]methionine)
- Drug information in FDA (Amino acid transporters, L-[^{11}C]methionine)

Synthesis

[PubMed]

A continuous flow procedure was automated for the synthesis of [^{11}C]methyl iodide from [^{11}C]CO_2 and L-[methyl-^{11}C]methionine from [^{11}C]methyl iodide and L-S-benzyl-homocysteine (8). The preparation was completed in 20 min after the end of bombardment with a yield of >30%. This procedure produced about 44 mCi or 1.62 MBq [^{11}C]MET with a specific activity of 3.3 Ci/mmol (122 GBq/mmol). Radiochemical purity is >96%.

A simple synthesis was performed without high-performance liquid chromatography (HPLC) purification (9), using a solid supported ^{11}C-methylation of L-homocysteine thiolactone on Al_2O_3. The preparation required only filtration for separation of L-homocysteine and [^{11}C]MET. Average absolute yields from 258 syntheses were 10.2 GBq (276 mCi), starting from 47.6 GBq (1.29 Ci) of [^{11}C]CO_2 at the end of bombardment, representing 21.2 ± 7.9%, not corrected for decay. The radiochemical purity was >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

There was a time dependent increase of uptake (0.73% at 0.5 h and 11% at 4 h) of [^{3}H]MET into HTB-14 human astrocytoma cells (10). [^{3}H]MET was incorporated into proteins (44%), lipid (2.6%), RNA (5.8%), and DNA (11%) at 4 h. About 35% of the radioactivity remained in free intracellular pool at 4 h.

[^{11}C]MET was found to be transported into F98 rat gliomas by the sodium independent transport system L (70%) and the Na^+-dependent system B^0 (30%) (6). About 15% of MET was incorporated into proteins at 2 h after incubation.

Animal Studies

Rodents

[PubMed]

Tissue accumulation of [^{11}C]MET was studied in nude mice with MCF-7 human breast carcinoma tumors at 1 h after injection of 0.37 MBq (0.01 mCi) of the tracer (11). The organ with the highest uptake was in the liver (8.02% injected dose (ID)/g), followed by the kidneys (7.60% ID/g), spleen (7.36% ID/g), and stomach (6.75% ID/g). The tumor, muscle, and blood uptakes were 2.60, 1.56, and 2.73% ID/g, respectively.

AH109A rat hepatoma tumor cells were inoculated subcutaneously into rats to study the effect of radiotherapy on protein synthesis (12). [^{11}C]MET was injected intravenously through the tail vein. The organ with the highest uptake was in the pancreas (7.5% ID/g), followed by the liver (4.5% ID/g). The tumor had an uptake of 2.7% ID/g and was clearly distinguished from other tissues. After 20 Gy (2,000 rads) of single-dose irradiation to the rat tumor, [^{11}C]MET uptake fell to 54 ± 19% of non-irradiated tumor uptake at 12 h after irradiation. Necrosis accounted for 49 ± 7% of total tissue volume after 3 days. Tumor volume decreased 48 ± 12% 10 days after irradiation. [^{11}C]MET uptake by tumor showed a sharp and rapid linear decrease after irradiation, and the response of the uptake to irradiation preceded the extension of necrosis and tumor shrinkage.

Other Non-Primate Mammals

[PubMed]

Muscle protein synthesis rates (PSRs) were measured by [^{11}C]MET PET in the paraspinal and hindlimb muscles of dogs (13). The PSRs were similar for paraspinal and hindlimb muscles, 0.172 and 0.208 nmol/min/g, respectively. The PSR determined by [^{3}H]MET measurements was 0.27 nmol/min/g, indicating <10% transmethylation of MET. In a later study in rats, the PSR was 0.22 nmol/min/g in normal rats and 0.0032 nmol/min/g in cycloheximide-treated rats, supporting the hypothesis that MET accumulates in skeletal muscle as ^{11}C-labeled proteins (14).

Non-Human Primates

[PubMed]

[^{11}C]-L- or [^{11}C]-D-methionine was injected intravenously into pregnant Rhesus monkeys (15). There was an instantaneous high uptake of radioactivity in the maternal aorta, and placenta. Both [^{11}C]-L- and D-methionine rapidly crossed the placenta and accumulated in the fetal liver. The fetal liver uptake of [^{11}C]-L-MET was higher than the [^{11}C]-D-MET. In the [^{11}C]-L-MET experiments, about 70% of the radioactivity in plasma was found in the high molecular fraction one hour after injection. A greater part of [^{11}C]-D-compared to [^{11}C]-L-activity was excreted in the urine. These data suggested that a major part of [^{11}C]-D-MET was not used in fetal liver for protein synthesis.

Human Studies

[PubMed]

Seventeen patients with suspected astrocytomas (9 of grade II and 8 of grade III) were studied by PET with [^{18}F]FDG and [^{11}C]MET (10). In all patients, PET images of [^{11}C]MET and [^{18}F]FDG provided higher tumor/white matter ratios than tumor/corresponding contralateral region ratios and tumor/mean cortical uptake ratios. In grade II patients, [^{18}F]FDG did not exhibit a significant increase in tumor uptake, whereas [^{11}C]MET was a good tumor predictor with ratios of about 1.50 ± 0.48. In grade III

patients, both [^{18}F]FDG and [^{11}C]MET exhibited higher uptake ratios than for grade II, with [^{11}C]MET(ratios of 2.50 ± 0.85) being better than [^{18}F]FDG, possibly suggesting enhanced protein synthesis.

[^{11}C]MET PET studies were performed the first 8 to 24 h after the onset of neurological symptoms and at the follow-up study 14 days after the ischemic attack (16). Increased [^{11}C]MET uptake was found significantly in patchy areas in the immediate vicinity of infarction as well as in distant areas within the same hemisphere. In those areas, regional cerebral blood flow and oxygen extraction fraction were highly variable, and the regional cerebral metabolic rate of oxygen was preserved or slightly reduced. It was postulated that there were alterations of amino acid transport or protein synthesis in the brain tissue because of either blood-brain barrier disruption or post-ischemic hyper-perfusion.

Human dosimetry of [^{11}C]MET was estimated in five normal volunteers (17). The average injected dose was 558 MBq (15.08 mCi). The organs that received the highest absorbed doses were found to be the bladder wall (0.027 mGy/MBq or 100 mrad/mCi), the pancreas (0.019 mGy/MBq or 70 mrad/mCi), the liver (0.018 mGy/MBq or 66 mrad/mCi), and the kidneys (0.011 mGy/MBq or 41 mrad/mCi). The effective dose was calculated as 0.0053 mSv/MBq (20 mrem/mCi) for a 70-kg-standard man.

For many years, [^{11}C]MET was used for brain imaging of gliomas, astrocytomas, oligodendrogliomas, and other malignant brain tumors [PubMed]. [^{11}C]MET PET is useful to evaluate low-grade brain tumors and their responses to treatment (18). However, about 20% of low-grade brain tumors were not detectable, and some infarcts, hematomas, and inflammatory tissues may show high uptake (3). [^{11}C]MET is proved to be a reliable and highly accurate imaging PET tracer for localizing parathyroid adenomas in patients in whom conventional imaging techniques have failed (19).

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