N-[*N*-[(*S*)-1,3-Dicarboxypropyl]carbamoyl]-*S*-[^{11}C]methyl-L-cysteine

[^{11}C]DCMC

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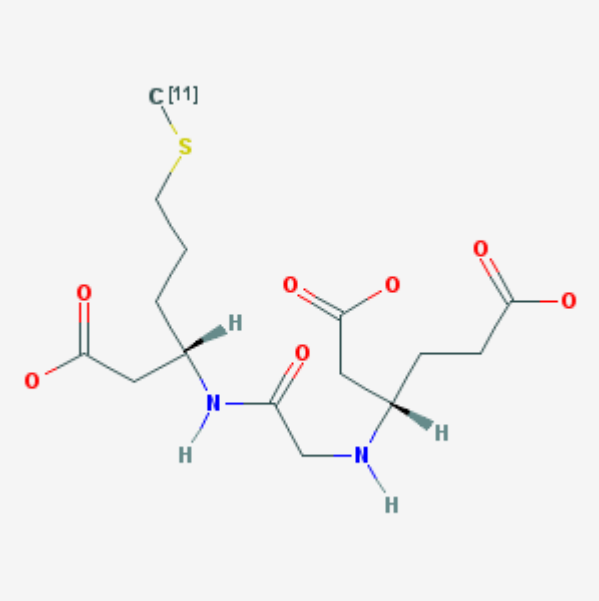
Chemical name:	*N*-[*N*-[(*S*)-1,3-Dicarboxypropyl]carbamoyl]-*S*-[^{11}C]methyl-L-cysteine
Abbreviated name:	[^{11}C]DCMC
Synonym:	[^{11}C]MCG
Agent Category:	Amino acid
Target:	Prostate-specific membrane antigen (PSMA)
Target Category:	Binding to PSMA
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

The prostate-specific membrane antigen (PSMA) is a cell-surface glycoprotein with a molecular weight of ~100 kDa. It is expressed predominantly in the prostate and has also been detected in other tissues such as the kidney, the proximal small intestine, and the salivary glands. Minimal expression has also been observed in the brain (1). It is believed that PSMA plays an important role in the progression of prostate cancer, glutamatergic neurotransmission, and in the absorption of folate (2). This glycoprotein is specifically upregulated several-fold in prostate cancers (PCAs), metastatic disease, and hormone-refractory PCAs because androgen levels inversely modulate PSMA levels (3). Interestingly, PSMA also has an elevated expression in the neovasculature of solid tumors, but is absent in normal neovasculature and prostate cancers tumors (4). Although its function in the prostate is unknown, in the central nervous system PSMA metabolizes *N*-acetyl-aspartyl-glutamate (NAAG), and in the proximal small intestine it removes γ-linked glutamates from poly-γ-glutamate folate and folate hydrolase (FOLH1), and also acts as a carboxypeptidase, glutamate carboxypaptidase II (GCPII) (1). Due to its unique distribution, PSMA can be used as a marker for the detection of metastatic cancers with imaging agents. Although a commercially available monoclonal antibody [^{111}In-Capromomab pendetide (ProstaScint)] is in clinical use for the detection of prostate cancer, the results obtained with this antibody are not entirely reliable (5). In addition, the antibodies have limited access to tumors and may produce low signal-to-noise ratios because the target is intracellular, whereas PSMA is present on the cell surface (6, 7). Therefore, a small molecule ^{11}C ligand, *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-*S*-[^{11}C]methyl-L-cysteine ([^{11}C]DCMC), was synthesized and evaluated for the imaging of PSMA-positive and -negative tumors using positron emission tomography (PET) in an *in vivo* rodent model for prostate cancer (8).

Synthesis

[PubMed]

N-[*N*-[(*S*)-1,3-Dicarboxypropyl]carbamoyl]-L-cysteine was used as a precursor for the synthesis of [^{11}C]DCMC (9, 10). The precursor (9) was dissolved in *N,N*-dimethylformamide (DMF), and a fresh DMF/ammonia solution was added to the solution and then followed by water (10). The solution was cooled to 20^{o}C and ^{11}C-labeled iodomethane was bubbled through it. The reaction contents were subsequently heated for 60 seconds in a 45^{o}C bath, and the reaction was terminated with acetonitrile/water/trifluoroacetic acid (6:94:0.075), followed by the addition of 20% trifluoroacetic acid (10). [^{11}C]DCMC was separated by high-performance liquid chromatography, reformulated in 0.9% saline, and sterile filtered. The specific radioactivity of [^{11}C]DCMC was determined and sterile sodium bicarbonate was added to the radioactive compound to bring the pH of the final formulation to ~7.0. The time for synthesis, including formulation, was ~30 min. Based on the amount of ^{11}C-labeled iodomethane used for the

synthesis, the yield of [^{11}C]DCMC was calculated to be 16% at the end of synthesis, with a purity of >97% (10) and specific radioactivity of 167 Gbq/μmol (4,000 Ci/mmol) within 30 min after bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The relative affinity of DCMC for PSMA was determined using the NAAG peptidase assay in membranes isolated from Chinese hamster ovary cells transfected with rat GCPII (11). For this assay, 4 μmol/L NAAG that contained trace amounts of ^{3}H-NAAG was incubated with the membranes in the presence of 0.1, 0.3, 1, 3, 10, 30, 100, 300, and 1,000 nmol/L DCMC. The NAAG hydrolysis product was separated by ion-exchange chromatography and determined by scintillation spectrophotometry (8). The K_i of DCMC for the NAAG activity was determined to be 1.9 nmol/L.

Animal Studies

Rodents

[PubMed]

The *in vivo* biodistribution of [^{11}C]DCMC was investigated in healthy (10) and xenograft-bearing mice (8).

Male CD-1 mice weighing 20 to 25 g received an injection of 100 μCi (3700 kBq) [^{11}C]DCMC in 200 μl saline through the tail vein (12). The mice were killed 5, 15, 30, 60, and 120 minutes after the injection. Brains were removed from the animals, and the cerebellum, olfactory bulb, hypothalamus, hippocampus, striatum, parietal cortex, brainstem, and the thalamus were harvested. The various tissues were weighed and the radioactivity was determined with an automated γ counter. For binding specificity, the mice were pretreated with doses of 1, 10, and 100 mg/kg 2-(phosphonomethyl)pentanedioic acid (PMPA), a potent inhibitor of GCPII (12), 5 minutes prior to the injection of [^{11}C]DCMC. The uptake of [^{11}C]DCMC was highest (61.0% of total) in the kidneys (which also have the highest GCPII concentration in the body) and was completely washed out by 120 minutes after administration. The prostate had a maximum of 2.55% uptake, probably because the mouse prostate has low levels of PSMA (10, 13). In this study, the brain, cerebellum, hippocampus, and cortex showed minimal incorporation of radioactivity. A target binding specificity of [^{11}C]DCMC was indicated because excess unlabelled DCMC or PMPA (up to 1 mg/kg) blocked uptake in the kidneys (10). In this study, the metabolites were determined at 5,15, 30, and 60 minutes after administration. The plasma and kidneys showed the highest metabolite levels, 9.2% and 10.4% of the total, respectively, at 60 minutes. This is probably because the metabolites bind to and are excreted through the kidneys.

The human LNCaP cell line (PSMA-positive) of human prostate cancer was used to develop the xenograft-bearing mouse (8). For PSMA-negative controls, animals with PC-3 (prostate cancer) and MCF-7 (breast cancer) cell xenografts were used. For the study, animals bearing xenografts (17–20 g) were injected through the tail vein either with 6.49 pmol, 200 μCi (7400 kBq) [^{11}C]DCMC alone or in combination with 50 mg/kg PMPA. Blood was collected immediately after animals were killed; select tissues were harvested and weighed, and absorbed radioactivity was counted in a γ counter. The biodistribution of [^{11}C]DCMC was highest in the LNCaP tumors, and tumors with MCF-7 or PC-3 cells exhibited significantly lower incorporation of radioactivity (8). Using excess amounts of PMPA as a blocking agent, these observations were confirmed with PET and planer γ scintigraphy imaging studies, respectively. Similar observations, as described above, were made with imaging of the kidneys (8).

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Renal cortical uptake and clearance studies of [^{11}C]DCMC were performed using PET in an ~30-kg adult male baboon, *Papio Anubis* (10). PET scanning was initiated immediately after an intravenous injection of 10 mCi (370 MBq) high specific activity [^{11}C]DCMC. Thirty-five simultaneous, contiguous, sequential, high-resolution quantitative tomographic slices of the brain were obtained over a 90-minute period. In addition, the animal was positioned so that the renal cortex was in complete view. This study showed there was significant uptake of [^{11}C]DCMC in the renal cortex of the animal, which was decreased by pretreatment with 2 mg/kg PMPA. Uptake of [^{11}C]DCMC in the brain was low and the authors concluded that [^{11}C]DCMC is not suitable to measure GCPII activity in the brain.

Human Studies

[PubMed]

No publications are currently available.

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