[^{11}C]Glycylsarcosine

[^{11}C]Gly-Sar

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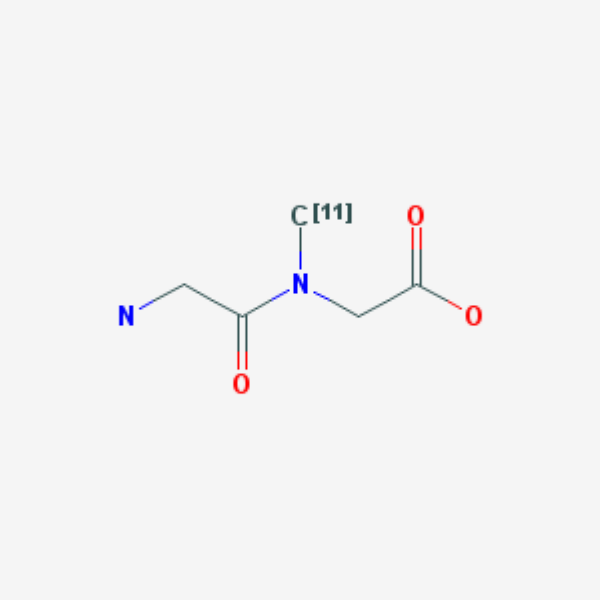
Created: September 21, 2008; Updated: November 17, 2008.

Chemical name:	[^{11}C]Glycylsarcosine
Abbreviated name:	[^{11}C]Gly-Sar
Synonym:	
Agent category:	Peptide
Target:	H^+/peptide transporters (PEPTs)
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal \contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

H^+/Peptide transporters (PEPTs) are members of the proton-coupled peptide transporter SLC15A family (1). PEPT1 is present in the epithelial cells of the small intestine, kidney, and bile duct, whereas PEPT2 is present in the epithelial cells of the kidney, lung,

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NLM Citation: Leung K. [^{11}C]Glycylsarcosine. 2008 Sep 21 [Updated 2008 Nov 17]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

mammary gland, and choroid plexus, as well as in glial cells in the brain (2, 3). PEPTs transport various peptides and peptide-mimetics. PEPT1 is overexpressed in some cancer cells. PEPT1 is expressed in the human fibrosarcoma HT1080 cell line but not in the normal fibroblast IMR-90 cell line (4). [^{11}C]Glycylsarcosine ([^{11}C]Gly-Sar) has been developed as a positron emission tomography (PET) tracer for imaging PEPTs in cancer cells (5, 6).

Synthesis

[PubMed]

Nabulsi et al. (6) synthesized [^{11}C]Gly-Sar in two steps. First, ^{11}C-methylation of glycylglycine ethyl ester with [^{11}C]methyl triflate was performed for 1 min at 170°C. A mixture of triethylamine and ammonium acetate was added to the reaction vial and heated for 5 min at 80°C to form [^{11}C]cyclo(Gly-Sar), which was purified with high-performance liquid chromatography. The radiochemical yield (decay-corrected) was 5.9% with >99% radiochemical purity. Second, [^{11}C]cyclo(Gly-Sar) was hydrolyzed with 2 N NaOH for 8 min at 100°C to form [^{11}C]Gly-Sar with a specific activity of 51.8 GBq/μmol (1.4 Ci/μmol), a radiochemical purity of >99%, and a radiochemical yield of 8.6% (decay-corrected, n = 8). The total synthesis time was 42 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro uptake studies were performed using AsPC-1, MKN45, and PC-3 cancer cell lines with 2 μM [^{3}H]Gly-Sar (5). The initial uptake rates were 3.88, 1.64, and 1.39 μL/min per mg protein, respectively. The presence of 20 mM Gly-Sar inhibited the uptake rates to 0.94, 0.77, and 1.22 μL/min per mg protein, respectively. The uptake of [^{3}H]Gly-Sar by these three cell lines correlated with their PEPT1 mRNA expression (AsPC-1 > MKN45 > PC-3).

Animal Studies

Rodents

[PubMed]

Nabulsi et al. (6) reported biodistribution studies of [^{11}C]Gly-Sar in normal mice (n = 4 mice/group). The mice showed high accumulation of radioactivity in the kidneys (~14% injected dose (ID)/g), followed by the spleen (~7% ID/g), lung (~3% ID/g), and liver (~2% ID/g) at 10 min after injectionthe pancreas was not studied) little accumulation was observed in the brain. Whole-body PET imaging confirmed the high accumulation in the kidney medulla. Mitsuoka et al. (5) performed biodistribution studies in nude mice bearing AsPC-1, MKN45, or PC-3 tumor xenografts. Tumor accumulation was rapid and reached a plateau 5–60 min after injection. The standard uptake values at 60 min were

0.70, 0.42, and 0.53, whereas the tumor/muscle ratios at 30 min were 5.0, 2.8, and 3.5 for AsPC-1, MKN45, and PC-3, respectively. High accumulation was found in the kidneys, followed by the pancreas, lung, and liver (the spleen was not studied). Whole-body PET imaging revealed high radioactivity in the kidneys and urinary bladder. All three tumors were clearly visualized. In another study, whole-body PET imaging was performed in nude mice bearing the AsPC-1 tumor xenografts and turpentine-induced inflammation in the opposite hind legs. [^{18}F]FDG was also used to compare with [^{11}C]Gly-Sar. The tumor/blood ratio (4.0) of [^{11}C]Gly-Sar was greater than the muscle/blood (1.7) and inflammation/blood (1.4) ratios. The inflammation/blood ratio (5.8) of [^{18}F]FDG was greater than the muscle/blood (1.3) and tumor/blood (4.0) ratios. The selectivity index (tumor/inflammation ratio corrected for normal muscle) was 25.1 for [^{11}C]Gly-Sar and 0.72 for [^{18}F]FDG. Immunohistochemistry of PEPT1 and PEPT2 studies confirmed the presence of PEPTs in all three tumor xenografts and kidneys, whereas inflammatory tissues and normal muscle were marginal for PEPTs. No blocking experiment was performed.

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.

Human Studies

CA009015, R01 GM035498

References

1. Herrera-Ruiz D., Knipp G.T. Current perspectives on established and putative mammalian oligopeptide transporters. J Pharm Sci. 2003;**92**(4):691–714. PubMed PMID: 12661057.
2. Groneberg D.A., Fischer A., Chung K.F., Daniel H. Molecular mechanisms of pulmonary peptidomimetic drug and peptide transport. Am J Respir Cell Mol Biol. 2004;**30**(3):251–60. PubMed PMID: 14969997.
3. Rubio-Aliaga I., Daniel H. Mammalian peptide transporters as targets for drug delivery. Trends Pharmacol Sci. 2002;**23**(9):434–40. PubMed PMID: 12237156.

4. Nakanishi T., Tamai I., Sai Y., Sasaki T., Tsuji A. Carrier-mediated transport of oligopeptides in the human fibrosarcoma cell line HT1080. Cancer Res. 1997;**57**(18): 4118–22. PubMed PMID: 9307302.
5. Mitsuoka K., Miyoshi S., Kato Y., Murakami Y., Utsumi R., Kubo Y., Noda A., Nakamura Y., Nishimura S., Tsuji A. Cancer detection using a PET tracer, 11C-glycylsarcosine, targeted to H+/peptide transporter. J Nucl Med. 2008;**49**(4):615–22. PubMed PMID: 18344442.
6. Nabulsi N.B., Smith D.E., Kilbourn M.R. [11C]Glycylsarcosine: synthesis and in vivo evaluation as a PET tracer of PepT2 transporter function in kidney of PepT2 null and wild-type mice. Bioorg Med Chem. 2005;**13**(8):2993–3001. PubMed PMID: 15781409.