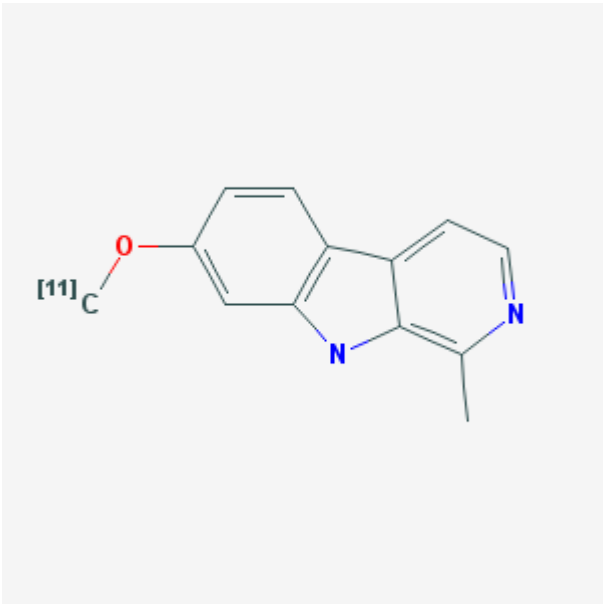
7-[^{11}C]Methoxy-1-methyl-9*H*-[3,4-*b*]indole

[^{11}C]HAR

Kam Leung, PhD[1]

Created: June 23, 2006; Updated: March 14, 2012.

Chemical name:	7-[^{11}C]Methoxy-1-methyl-9*H*-[3,4-*b*]indole
Abbreviated name:	[^{11}C]HAR
Synonym:	[^{11}C]Harmine
Agent category:	Compound
Target:	Monoamine oxidase A (MAO-A)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-primate non-rodent mammals • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

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

Corresponding author.

NLM Citation: Leung K. 7-[^{11}C]Methoxy-1-methyl-9*H*-[3,4-*b*]indole. 2006 Jun 23 [Updated 2012 Mar 14]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Monoamine oxidase (MAO) is a mitochondrial enzyme which inactivates dopamine, noradrenaline and serotonin in the brain (1, 2). Two isoforms (A and B) of the enzyme have been identified. MAO-A preferentially oxidizes serotonin and noradrenaline, whereas MAO-B preferentially oxidizes phenethylamine. Dopamine is a substrate for both enzymes. MAO-A is predominately associated with depression and anxiety disorders while MAO-B is predominately associated with neurodegenerative disease, such as Parkinson's disease (PD) as indicated by studies with specific MAO isoform inhibitors (3-5).

For measurements of MAO-A activity, MAO-A inhibitor harmine (HAR) was radiolabeled as [^{11}C]HAR for use in positron emission tomography (PET). HAR is a carboline analog, which is a competitive and reversible inhibitor of MAO-A with a K_i of 5 nM (6). [^{11}C]HAR is being developed as a PET agent for the non-invasive study of brain MAO-A distribution and concentration in patients with psychiatric and neurologic disorders as well as neuroendocrine tumors.

Related Resource Links:

- Chapters in MICAD (MAO-A, MAO-B)
- Gene information in NCBI (MAO-A, MAO-B)
- Articles in Online Mendelian Inheritance in Man (OMIM) (MAO-A, MAO-B)
- Clinical trials (MAO-A, MAO-B)
- Drug information in FDA (MAO-A, MAO-B)

Synthesis

[PubMed]

Bergstrom et al. (7) reported synthesis of [^{11}C]HAR by direct O-methylation of 7-hydroxy-1-methyl-9*H*-[3,4-*b*]indole with [^{11}C]methyl iodide in the presence of sodium hydroxide in DMSO, with a radiochemical yield of 72.5 ± 3.6% (end of synthesis) after high-performance liquid chromatography purification. Radiochemical purities were >98% with a specific activity of 18-93 GBq/μmol (0.5-2.5 Ci/μmol) and a total synthesis time of 43 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Bergstrom et al. (8) reported that [^{11}C]HAR bound rapidly to frozen sections of rat brain with a K_d of 2.0 ± 0.7 nM. The binding was reversible by washings. There were about 14-22% non-specific binding, which could not be displaced by 1 μM of HAR. The specific

binding was inhibited by various MAO-A inhibitors, such as clorgyline (IC_{50} = 16 nM), esuprone (IC_{50} = 19 nM), and brofaromine (IC_{50} = 50 nM). On the other hand, MAO-B inhibitors (deprenyl and pargyline) were inhibitory only at >1 μM concentrations.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

Jensen et al. (9) reported on PET studies in five adult female Gottingen minipigs with [^{11}C]HAR under baseline conditions and after pargyline (a 20-fold more potent inhibitor of MAO-B than of MAO-A). Distribution volumes (DVs) of [^{11}C]HAR relative to the arterial input were estimated from parametric images of brain regions of interest. The medial hypothalamus (139 ml/g) and ventral forebrain (139 ml/g) had the highest [^{11}C]HAR binding, followed by the thalamus (135 ml/g), locus coeruleus (133 ml/g), striatum (104 ml/g), pituitary (92 ml/g), frontal cortex (91 ml/g), occipital cortex (84 ml/g), and cerebellum (74 ml/g). Pargyline pretreatment (6 mg/kg) reduced the magnitude of DV globally to 34-54 ml/g. Nearly complete inhibition of [^{11}C]HAR binding was detected in the occipital cortex, frontal cortex, and striatum, but there was 15-35% of [^{11}C]HAR binding resistant to pargyline inhibition in the pituitary gland and diencephalon.

Non-Human Primates

[PubMed]

Bergstrom et al. (7, 8) performed [^{11}C]HAR PET studies in rhesus monkeys and found rapid accumulation in the brain within minutes after injection. The accumulation of [^{11}C]HAR showed high radioactivity in all gray matter regions homogeneously, with a standard uptake value (SUV) of 2.5 at 3.5 min and a final value of 3.7 at 60 min. Pretreatments with various MAO-A inhibitors decreased the SUV to 2.3 at 60 min. Patlak graphic analysis estimated an IC_{50} value of 0.05-0.1 mg/kg for blocking of [^{11}C]HAR uptake by HAR in the brain.

Human Studies

[PubMed]

Bergstrom et al. (10) studied 16 healthy male volunteers with [^{11}C]HAR PET before and after pretreatment with esuprone (n = 8), moclobemide (n = 4) and placebo (n = 4). The

subject was given 200-300 MBq (5.4-9.1 mCi) of [^{11}C]HAR with plasma metabolite samplings. The accumulation of [^{11}C]HAR in the brain was high in all grey matter regions, with minor differences between different regions of the brain. Patlak graphic analyses revealed an 80% inhibition of [^{11}C]HAR binding in the grey matter regions by esurprone and moclobemide. Later, Ginovart et al. (11) confirmed the moclobemide inhibition using a two-tissue compartment model to estimate DV values in regions of interest in the brain. [^{11}C]HAR uptake was highest in the thalamus, followed by the temporal cortex=cingulated, occipital cortex, frontal cortex=putamen, and cerebellum. The estimated DV values were highly stable and not different from those estimated with the Logan analyses. There was a 64-79% reduction of [^{11}C]HAR binding in the brain after dosing with moclobemide (300 mg daily for 10 days). The fraction of unchanged [^{11}C]HAR in the plasma was 90% at 5 min, 46% at 20 min, and 34% at 30 min.

Orlefors et al. (12) showed [^{11}C]HAR PET could visualize tumors in 11 patients with midgut carcinoids (MGC) and endocrine pancreatic tumors (EPT). The mean SUV for MGC (n = 4) at 5 min was 7.5 ± 3.9 and for EPT (n = 7) 12.9 ± 2.7, whereas the SUV for normal liver, intestine and pancreas were 3.1 ± 0.5, 3.4 ± 1.2 and 8.9 ± 3.0, respectively.

References

1. Richards J.G., Saura J., Ulrich J., Da Prada M. *Molecular neuroanatomy of monoamine oxidases in human brainstem.* Psychopharmacology (Berl). 1992;106 Suppl:S21–3. PubMed PMID: 1546134.
2. Saura J., Kettler R., Da Prada M., Richards J.G. *Quantitative enzyme radioautography with 3H-Ro 41-1049 and 3H-Ro 19-6327 in vitro: localization and abundance of MAO-A and MAO-B in rat CNS, peripheral organs, and human brain.* J Neurosci. 1992;12(5):1977–99. PubMed PMID: 1578281.
3. Murphy D.L., Wyatt R.J. *Reduced monoamine oxidase activity in blood platelets from schizophrenic patients.* Nature. 1972;238(5361):225–6. PubMed PMID: 4558353.
4. Murphy D.L., Weiss R. *Reduced monoamine oxidase activity in blood platelets from bipolar depressed patients.* Am J Psychiatry. 1972;128(11):1351–7. PubMed PMID: 5020182.
5. Jarman J., Glover V., Sandler M., Turjanski N., Stern G. *Platelet monoamine oxidase B activity in Parkinson's disease: a re-evaluation.* J Neural Transm Park Dis Dement Sect. 1993;5(1):1–4. PubMed PMID: 8439389.
6. Kim H., Sablin S.O., Ramsay R.R. *Inhibition of monoamine oxidase A by beta-carboline derivatives.* Arch Biochem Biophys. 1997;337(1):137–42. PubMed PMID: 8990278.
7. Bergstrom M., Westerberg G., Kihlberg T., Langstrom B. *Synthesis of some 11C-labelled MAO-A inhibitors and their in vivo uptake kinetics in rhesus monkey brain.* Nucl Med Biol. 1997;24(5):381–8. PubMed PMID: 9290071.
8. Bergstrom M., Westerberg G., Langstrom B. *11C-harmine as a tracer for monoamine oxidase A (MAO-A): in vitro and in vivo studies.* Nucl Med Biol. 1997;24(4):287–93. PubMed PMID: 9257326.

9. Jensen S.B., Olsen A.K., Pedersen K., Cumming P. *Effect of monoamine oxidase inhibition on amphetamine-evoked changes in dopamine receptor availability in the living pig: a dual tracer PET study with [11C]harmine and [11C]raclopride.* Synapse. 2006;59(7):427–34. PubMed PMID: 16485265.
10. Bergstrom M., Westerberg G., Nemeth G., Traut M., Gross G., Greger G., Muller-Peltzer H., Safer A., Eckernas S.A., Grahner A., Langstrom B. *MAO-A inhibition in brain after dosing with esuprone, moclobemide and placebo in healthy volunteers: in vivo studies with positron emission tomography.* Eur J Clin Pharmacol. 1997;52(2): 121–8. PubMed PMID: 9174681.
11. Ginovart N., Meyer J.H., Boovariwala A., Hussey D., Rabiner E.A., Houle S., Wilson A.A. *Positron emission tomography quantification of [11C]-harmine binding to monoamine oxidase-A in the human brain.* J Cereb Blood Flow Metab. 2006;26(3): 330–44. PubMed PMID: 16079787.
12. Orlefors H., Sundin A., Fasth K.J., Oberg K., Langstrom B., Eriksson B., Bergstrom M. *Demonstration of high monoaminoxidase-A levels in neuroendocrine gastroenteropancreatic tumors in vitro and in vivo-tumor visualization using positron emission tomography with 11C-harmine.* Nucl Med Biol. 2003;30(6):669–79. PubMed PMID: 12900293.