[^{11}C]*meta*-Hydroxyephedrine

[^{11}C]mHED

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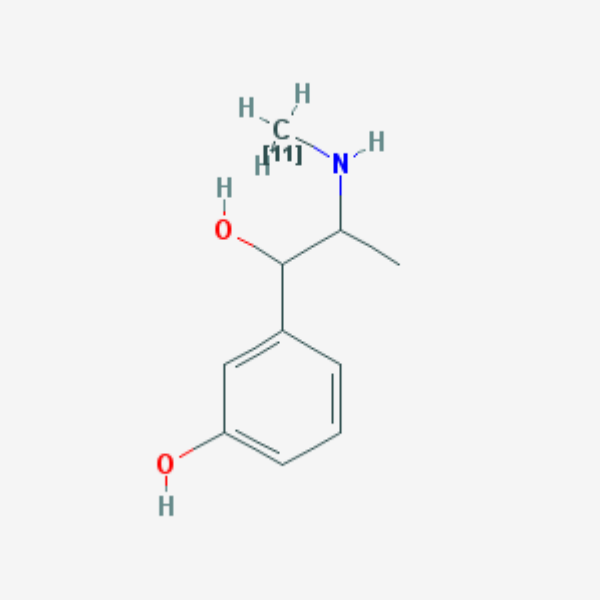
Created: January 19, 2006; Updated: June 30, 2008.

Chemical name:	[^{11}C]*meta*-Hydroxyephedrine
Abbreviated name:	[^{11}C]mHED
Synonym:	(1*R*,2*S*)-[^{11}C]*meta*-Hydroxyephedrine; [^{11}C]HED; [*N-methyl* ^{11}C]*meta*-Hydroxyephedrine
Agent Category:	Compound
Target:	Norepinephrine transporter (NET), vesicular monoamine transporter (VMAT), neuronal storage vesicle
Target Category:	Transporter binding and storage in the sympathetic nervous system (SNS)
Method of detection:	Positron emission tomography (PET)
Source of signal/ contrast:	^{11}C
Activation:	No



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Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans	Click on the above structure for additional information in PubChem.

Background

[PubMed]

[^{11}C]-*meta*-Hydroxyephedrine ([^{11}C]mHED) is a radioligand developed for positron emission tomography (PET) imaging of the sympathetic nervous system (SNS). It is a catecholamine analog labeled with ^{11}C, a positron emitter with a physical $t_{½}$ of 20.4 min (1).

Many diseases affect the SNS, and imaging of pathologic changes of adrenergic transmission has been an important area of PET research (2, 3). Most postganglionic sympathetic neurons in the autonomic nervous system release the neurotransmitter, norepinephrine (NE), which stimulates adrenergic receptors of various effector organs (4). There are different types of adrenergic receptors, and NE stimulates α_1, β_1 and certain β_2 receptors. The NE transporter (NET) is a transmembrane protein located in the adrenergic nerve terminals that is responsible for active reuptake (uptake-1) of NE released from neurons (5). NE is stored in the neuronal vesicles and is released on stimulation. Significant expression of NET is found in major organs of the SNS such as the heart and brain. There is substantial evidence that aberrations in cardiac SNS function contribute to the morbidity and mortality associated with cardiac diseases (6).

Molecular probes with structures closely related to NE can be used to assess the integrity of presynaptic sympathetic nerve terminals in various diseases. [^{123}I]*meta*-iodobenzylguanidine ([^{123}I]MIBG), a single-photon emission tomography (SPECT) agent, has been developed and used for neuronal imaging. Efforts have been made to develop a posiron-emitting tracer because of the inadequate quantitative information and lower spatial resolution obtained by SPECT imaging with MIBG. [^{11}C]mHED was

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NLM Citation: Cheng KT. [^{11}C]*meta*-Hydroxyephedrine. 2006 Jan 19 [Updated 2008 Jun 30]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

developed based on metaraminol, a synthetic false transmitter analog of NE, that accumulates in nerve terminals in the same way as NE (1, 7). Metaraminol is released by nerve stimulation but only has weak postsynaptic effects. Unlike NE, metaraminol is not metabolized by catechol–*O*–methyl transferase (COMT). The α methyl group on the side chain of metaraminol also renders the compound resistant to oxidative deamination by monoamine oxidase (MAO). [^{11}C]mHED is a metaraminol analog and is a good substrate for the NET. It shares the same neuronal uptake mechanism as NE and is also resistant to metabolism by COMT and MAO. Retention of [^{11}C]mHED in the NET-expressing tissue appears to be the result of rapid NET-mediated reuptake of the radiotracer.

Synthesis

Rosenspire et al. (1) synthesized [^{11}C]mHED by direct N-methylation of metaraminol for heart neuronal imaging. The precursor compound, metaraminol free base, was prepared from the commercially available metaraminol bitartrate salt. [^{11}C]Methyl iodide obtained from the ^{14}N(p.α)^{11}C reaction was reacted with metaraminol in dimethylformamide/dimethyl sulfoxide (3:1) at 100 °C for 5 min. The product was purified by high performance liquid chromatography (HPLC) using a C-18 reverse-phase column. [^{11}C]mHED was produced with a specific activity of 33.3 ± 18 GBq/μmol (900 ± 487 Ci/mmol) at the end of synthesis (EOS) and a total synthesis time of 45 min. The corrected radiochemical yield was 40-50%, and the radiochemical purity was >98%. The stereoisomer form prepared by this method was the (–) erythro isomer, 1*R*,2*S*-(–)MHED.

Nagren K et al. (8) used [^{11}C]methyl triflate to prepare [^{11}C]mHED. [^{11}C]methyl triflate was prepared by reacting [^{11}C}methyl iodide with silver triflate impregnated graphitized carbon at 150-200 °C. Metaraminol in acetonitrile was reacted with [^{11}C]methyl triflate at 60 °C for 1 min, and the product was purified by reversed-phase HPLC. The study reported a decay-corrected radiochemical yield of 65-75%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

DeGrado et al. (9) investigated the retention mechanisms of [^{11}C]mHED (specific activity >55,500 GBq/mmol or >1500 Ci/mmol) and interactions with NE in isolated rat hearts. They found a strong uptake process (K_1 = 2.66 ± 0.39 ml/g/min; n = 5) in the heart and a relatively slow clearance rate (k_2 = 0.011 ± 0.003 min^{-1}). NE appeared to increase the clearance rate (k_2 = 0.016 ± 0.009 min^{-1} at 5 nM and 0.034 ± 0.016 min^{-1} at 10 nM) without affecting initial uptake rates (K_1 = 2.81 ± 0.25 ml/g/min at 5 nM and 2.53 ± 0.67 ml/g/min at 10 nM). In the presence of 40 nM desipramine (DMI), a potent inhibitor of NET, [^{11}C]mHED uptake was blocked. The study indicated that the uptake and retention of [^{11}C]mHED by the heart was specific to sympathetic nerve terminals. Caldwell et al. (6) used isolated perfused rat hearts to demonstrated that an axially distributed blood-

tissue exchange model could be used for the quantitation of cardiac presynaptic SNS function with [^{11}C]mHED.

Buursma et al. (5) studied the potential of using NET as a reporter gene and [^{11}C]mHED as a reporter probe for gene therapy in *in vitro* cell lines of green monkey kidney (COS-7), human glioma (U373), and the human kidney (HEK293). The cells were transiently transduced with an adenoviral vector (AdTrack-hNET). In all 3 cell lines, [^{11}C]mHED cellular uptake was positively correlated with AdTrack-hNET viral titer ($r^2 \geq 0.949$; $P < 0.05$) and enhanced fluorescence of the green fluorescent protein (as a substitute for a therapeutic gene; $r^2 \geq 0.965$; $P < 0.005$). Human NET (hNET) protein expression was positively correlated ($r^2 = 0.987$, $P < 0.0001$) with [^{11}C]mHED uptake in U373 cells. In the presence of DMI, [^{11}C]mHED uptake was reduced to the level in control cells (cells infected with control virus).

Animal Studies

Rodents

Rosenspire et al. (1) studied the biodistribution of [^{11}C]mHED in rats, using doses of 1850-7400 kBq (50-200 μCi) doses. There was preferential uptake of [^{11}C]mHED in organs with rich adrenergic innervation (heart, spleen, and adrenals). The radioactivities (as percentage injected dose per g, (% ID)/g; $n = 4$) in the heart ventricles, spleen, adrenals, liver, kidney, and blood were 3.46 ± 0.47, 1.42 ± 0.56, 1.30 ± 0.12, 2.01 ± 0.34, 3.81 ± 8.70, and 0.13 ± 0.01, respectively, at 5 min. At 30 min, these values were 2.69 ± 0.10, 1.11 ± 0.08, 0.90 ± 0.20, 2.22 ± 0.19, 0.62 ± 0.10, and 0.07 ± 0.01% ID/g, respectively. Radioactivity cleared more rapidly from the lung than from the liver. The heart/liver and heart/lung ratios were 1.2 and 6.6 at 30 min, respectively. The heart/blood ratios at 5 and 30 min were 26 and 35, respectively. When DMI (10 mg/kg) was given to the rats before [^{11}C]mHED administration, the radioactivities (as % ID/g) in the heart ventricles, spleen, and adrenal, as compared to those of the untreated rats, were significantly decreased by 92%, 74%, and 62%, respectively,

Law et al. (10) assessed the biodistribution and metabolism of [^{11}C]mHED (specific activity = 15-36 GBq/μmol or 0.41-0.97 Ci/μmol at EOS) in rats with doses of 3-30 MBq (0.08-0.8 mCi)/0.8-1.5 nmol/kg. The radioactivity decreased rapidly in the plasma during the first 2 min and then remained relatively constant for the next 60 min. Uptake in the brain was low. Tissue to plasma ratios (tissue cpm x g^{-1}/plasma cpm x g^{-1}) for myocardium, liver, lung, kidney. and muscle were 36 ± 2, 22 ± 2, 6.0 ± 0.5, 4.1 ± 0.7, and 1.9 ± 0.2, respectively. Co-injection of unlabeled mHED or metaraminol bitartrate decreased myocardium radioactivity, but not in other tissues. No difference was found between the *in vivo* binding potential for mHED and metaraminol in the myocardium. Analyses of rat plasma and liver samples revealed 6 radioactive metabolites that were more polar than [^{11}C]mHED. No metabolites were detected in myocardium samples. In the plasma, 90% of radioactivity at 2.5 min was [^{11}C]mHED, which decreased to 15% at

60 min. In the heart, 99.3% of the radioactivity was [^{11}C]mHED and the percentage remained unchanged at 60 min.

Buursma et al. (5) used rats bearing U373 s.c. tumor to study the feasibility of using [^{11}C]mHED as a reporter gene probe. Tumor-bearing rats received injections of AdTrack-hNET adenovirus 2 days before [^{11}C]mHED imaging. Averaged [^{11}C]mHED uptake in hNET- transfected tumors (0.13 ± 0.02% ID/g) was significantly higher ($P < 0.05$) than in the controls (0.11 ± 0.01% ID/g).

Other Non-Primate Mammals

[PubMed]

A metabolic fate study in guinea pigs showed that most of the radioactivity in the heart, liver and blood remained as [^{11}C]mHED at 5 min (1). By 30 min, over 50% of liver radioactivity came from metabolites of [^{11}C]mHED but >95% radioactivity in the heart remained as [^{11}C]mHED. Caldwell et al. (6) showed the feasibility of using [^{11}C]mHED imaging to evaluate the presynaptic cardiac sympathetic function in a dog. Hutchins et al. (11) used [^{11}C]mHED PET imaging to study sympathetically denervated canine myocardium in dogs and concluded that regional sympathetic denervation altered oxidative metabolism but not perfusion.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Schwaiger et al (12) evaluated [^{11}C]mHED heart imaging in 6 normal volunteers and 5 patients. The specificity activity of [^{11}C]mHED was >37,000 GBq (1,000 Ci)/mmol at EOS, and each patient received a dose of 740 MBq (20 mCi). The heart/blood and heart/lung activity ratios in normal volunteers at 30 min after administration were 5.0 and 4.2, respectively. The myocardial activity retention (as the percentage of initial peak activity) decreased from 43 ± 18% at 1 min to 33 ± 16% at 2 min but remained constant (35 ± 13%) up to 60 min. The retention of radioacetivity in the myocardium was markedly reduced in cardiac transplant patients, retention was with 52 ± 17% of the initial peak value at 1 min and decreased to 26 ± 8% at 2 min and 9 ± 3% at 60 min. Ziegler et al. (13) studied the relationship between regional [^{11}C]mHED activity and the functional sympathetic innervation of the left ventricle as measured by heart rate variability spectral analysis in 12 cardiac transplant patients. The study showed regional increases in [^{11}C]mHED radioactivity and retention (uptake and storage) in patients who demonstrated functional innervation.

A retrospective study by Pietila et al. (14) of 46 patients with chronic heart failure (CHF) indicated that CHF patients had significantly (P<0.0001) lower retention of [^{11}C]mHED (0.184 ± 0.061; retention index = myocardium activity/integral of time-activity curve in plasma) than healthy subjects (0.283 ± 0.044). Patients with poor prognosis (death or transplantation) had even lower retention (0.137 ± 0.041; *n* = 11). Various other studies have shown the potential clinical utility of [^{11}C]mHED in evaluating cardiac sympathetic innervation affected by various diseases [PubMed].

Shulkin et al. (15) used [^{11}C]mHED to image pheochromocytoma in 10 patients with known or suspected pheochromocytoma. The radioactivity was rapidly taken up by the tumors, and most tumors were evident within 2-5 min. The tumor activity was unrelated to plasma catecholamine values at the time of administration. There was also prompt radioactivity localization in the liver and kidney. Whereas the liver activity remained constant, the kidney activity rapidly decreased after 4 min. In a study of 12 patients, Trampal et al. (16) found that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of [^{11}C]mHED imaging in the detection of pheochromocytoma were 92%, 100%, 100%, 87.5%, and 95%, respectively. In another study (17), neuroblastoma was located by PET imaging with [^{11}C]mHED (185 MBq (5 mCi) for children) in 7 patients. Tumor activity was evident in imaging within 5 min after administration.

NIH Support

NIH HL27555, NIMH 41205-7, NCI-5-P32-CA09015, R01 HL41047-01, R01 HL27555-06, HL 52323, NCI R29 CA54216 01.

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