1*R*-[^{11}C]Phenylephrine

[^{11}C]PHEN

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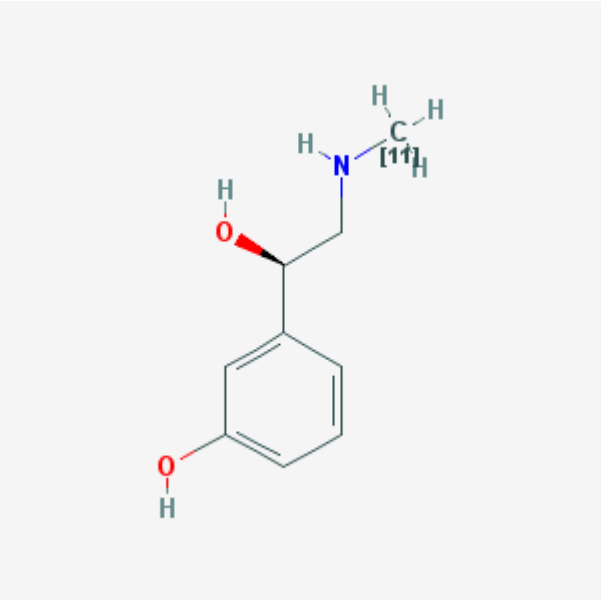
Chemical name:	1*R*-[^{11}C]Phenylephrine
Abbreviated name:	[^{11}C]PHEN
Synonym:	(–)-[^{11}C]Phenylephrine
Agent Category:	Compound
Target:	Norepinephrine transporter (NET), vesicular monoamine transporter (VMAT2), neuronal storage vesicle, monoamine oxidase (MAO)
Target Category:	Transporter binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal/ contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans



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Background

PubMed]

1*R*-[^{11}C]Phenylephrine ([^{11}C]PHEN) 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, 2).

Many diseases affect the SNS, and imaging of the pathologic changes of adrenergic transmission has been an important area of PET research (3, 4). Most postganglionic sympathetic neurons in the autonomic nervous system release the neurotransmitter, norepinephrine (NE), which stimulates adrenergic receptors in various effector organs (5). 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 by neurons (6). 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 (7).

Molecular probes with structures closely related to NE can be used to assess the integrity of presynaptic sympathetic nerve terminals in various diseases. *meta*-Iodobenzylguanidine ([^{123}]MIBG), a single-photon emission tomography (SPECT) agent, has been developed and used for neuronal imaging (2). Efforts have been made to develop a positron-emitting tracer because of the inadequate quantitative information and lower spatial resolution obtained by SPECT imaging with MIBG. [^{11}C]*meta*-Hydroxyephedrine ([^{11}C]mHED) was first developed based on metaraminol, a synthetic false transmitter analog of NE, that accumulates in nerve terminals in the same way as NE (8). [^{11}C]PHEN is structurally similar to [^{11}C]mHED and lacks only the α-methyl group. This difference appears to render [^{11}C]PHEN susceptible to oxidative deamination by axoplasmic monoamine oxidase (MAO). Thus, [^{11}C]PHEN is transported into sympathetic nerve varicosities by NET and taken up into storage vesicles (9, 10). It is most likely cleaved by MAO at the α-carbon into two by-products: an unlabeled aldehyde and [^{11}C]methylamine. [^{11}C]Methylamine is a freely diffusible molecule that rapidly leaves the neuron and enters the systemic circulation. In principle, heart PET imaging with [^{11}C]PHEN may allow the assessment of heart MAO activity.

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Synthesis

[PubMed]

Del Rosario et al. (1) synthesized [^{11}C]PHEN from the precursor of (−)-*m*-octopamine. (±)-*m*-Octopamine was obtained commercially and converted to the anhydrous free-base form with use of O,O-dibenzoyl (+)-tartartic acid for separation. Repeated recrystallization produced (−)-*m*-octopamine as the dibenzoyl (+)-tartrate salt with >94-96% enantiomeric purity. (−)-*m*-Octopamine was methylated with either CH_3I or $CF_3SO_3{}^{11}CH_3$. For best yield, Del Rosario et al. (1) trapped gaseous $CF_3SO_3{}^{11}CH_3$ at −40 °C in a solution of (−)-*m*-octopamine (~1 mg/300 µl in anhydrous dimethylformamide). The mixture was warmed to room temperature in 2 min and then purified by strong cation-exchange high-performance liquid chromatography (HPLC). The specific activity was >18,500 GBq (500 Ci)/mmol at the end of synthesis (EOS). Radiochemical yield was >50% at EOS, and radiochemical purity was >97%. Chiral purity was >94-96%, as determined by copper Schiff-base chiral HPLC.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Raffel et al. (11) studied the metabolism and kinetics of [^{11}C]PHEN in *in vitro*-isolated working rat hearts. [^{11}C]PHEN with a specific activity >18,500 GBq (500 Ci)/mmol at EOS was used. [^{11}C]D2-PHEN, a [^{11}C]PHEN analog with deuterium replacement of the two hydrogen atoms on the α-carbon of the PHEN side chain to slow MAO activity at the tracer level, was used in the experiment. The initial uptake rates (K_{up}, ml/min/g wet weight) for [^{11}C]PHEN (n = 11) and [^{11}C]D2-PHEN (n = 6), were not significantly different: 0.72 ± 0.15 and 0.82 ± 0.10, respectively. Treatment with pargyline (100 µM; MAO inhibitor) did not change the uptake rate of [^{11}C]PHEN, but treatment with reserpine (vesicular uptake inhibitor) decreased the uptake rates of both [^{11}C]PHEN and [^{11}C]D2-PHEN. The washout half-times (sum of three exponential terms) for [^{11}C]PHEN and [^{11}C]D2-PHEN were significantly different: 98.2 ± 13.7 and 163.2 ± 39.0 min, respectively. In the presence of pargyline, reserpine, and pargyline+reserpine, the $t_{½}$ of [^{11}C]PHEN decreased to 140.4 ± 27.8, 31.2 ± 6.0, and 14.9 ± 1.3 min, respectively. In the presence of reserpine, the $t_{½}$ of [^{11}C]D2-PHEN decreased to 14.6 ± 3.4 min. The study concluded that [^{11}C]PHEN kinetics were sensitive not only to neuronal MAO activity but also to changes in neuronal vesicular storage function.

Animal Studies

Rodents

[PubMed]

A tissue distribution study of [^{11}C]PHEN in rats was conducted by Del Rosario et al. (1) with a dose of 2.7-5.4 kBq (100-200 µCi). At 30 min, major organs with high radioactivity

were the heart, liver, and spleen. The percent of injected dose per g (% ID/g) values for the ventricles, liver, lung, spleen, kidney, and blood at 30 min were 1.45 ± 0.25, 1.51 ± 0.15, 0.62 ± 0.09, 1.30 ± 0.20, 1.01 ± 0.31, and 0.23 ± 0.02, respectively. Approximately 2.44% ID accumulated in the submaxillary gland at 30 min. More than 50% of the radioactivity present in the heart at 5 min was cleared from the heart by 60 min. In comparison, [^{11}C]PHEN showed lower initial heart uptake and faster heart clearance than [^{11}C]mHED. The study also showed that [^{3}H]phenylephrine (^{3}H on position 4 of the phenyl ring) and [^{11}C]PHEN had similar heart efflux rates. Very low brain extraction (0.06% ID) at 30 min was observed. Pretreatment with desipramine (DMI), a specific blocker, showed blockade for the ventricles and atria ranging from 72 to 77%. After treatment with clorgyline, a selective MAO (isoform A) inhibitor, the heart radioactivity levels were higher at 15 and 60 min than those in untreated rats.

Other Non-Primate Mammals

[PubMed]

Del Rosario et al. (1) reported the heart time-activity curves and PET images of [^{11}C]PHEN in dogs. PET heart images at 30-60 min indicated relatively fast clearance of radioactivity from the heart. The time–activity profile in dogs appeared to be similar to that in rats. Raffel et al. (10) reported no significant differences between the kinetics of [^{11}C]PHEN and [^{11}C]D2-PHEN in dogs. The authors suggested that there was considerable species variability in cardiac MAO and that MAO levels in the canine heart were very low. Thus, dogs could be a problematic animal model for studying MAO sensitivity.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Raffel et al. (9) performed cardiac PET studies with [^{11}C]PHEN in 14 healthy volunteers. The specific activity of [^{11}C]PHEN was >18.5 TBq (500 Ci)/mmol at EOS, and the dose was 740 MBq (20 mCi). Tandem studies with [^{11}C]mHED were performed in 10 patients. The relative myocardial distributions of [^{11}C]PHEN and [^{11}C]mHED were similar, but [^{11}C]PHEN cleared from the myocardium with an average $t_{½}$ of 58 ± 5.2 min, whereas [^{11}C]mHED activity remained constant for the 40-60 min of imaging time. The retention index (tissue activity/arterial blood activity ratio, as ml blood/min/ml tissue, based on PET images) values of [^{11}C]PHEN were approximately half those of [^{11}C]mHED. These values were significantly correlated when corrections for blood [^{11}C]PHEN metabolites (appeared at approximately 3 times the rate of [^{11}C]mHED) were made. After oral DMI

oral administration (two 50-mg doses), there were marked decreases in myocardial activity of both radioligands. Mean reductions of both radioligands were not significantly different.

In another study, Raffel and Wieland (10) conducted paired PET experiments with [^{11}C]PHEN and [^{11}C]D2-PHEN in 6 normal volunteers. The retention indexes at 40-60 min for [^{11}C]PHEN and [^{11}C]D2-PHEN were 0.066 ± 0.011 and 0.086 ± 0.018, respectively. The washout half-times for [^{11}C]PHEN and [^{11}C]D2-PHEN were 59 ± 10 and 155 ± 52 min, respectively. The authors concluded that the *in vivo* kinetics of [^{11}C]PHEN were sensitive to neuronal MAO activity in the human heart. Because vesicular storage of [^{11}C]PHEN protected it from MAO metabolism, [^{11}C]PHEN kinetics were also dependent on vesicular storage function.

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