R-(–)-[^{11}C]Epinephrine

[^{11}C]EPI

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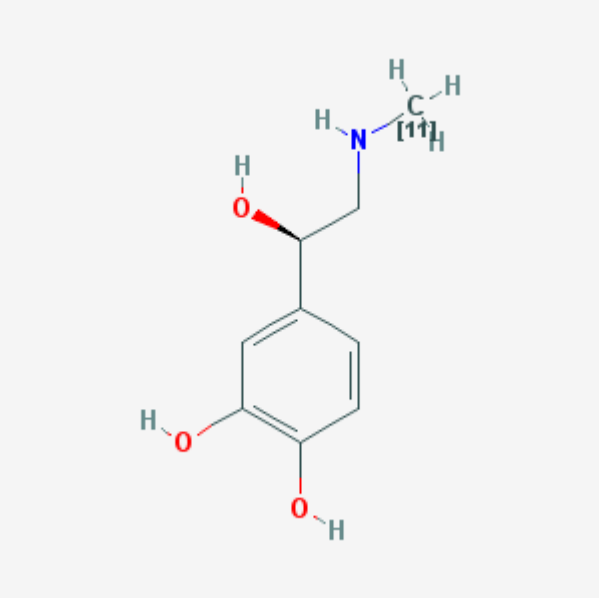
Chemical name:	*R*-(–)-[^{11}C]Epinephrine
Abbreviated name:	[^{11}C]EPI
Synonym:	[^{11}C]Epinephrine
Agent Category:	Compound
Target:	Norepinephrine transporter (NET), vesicular monoamine transporter (VMAT), neuronal storage vesicle, monoamine oxidase (MAO), catechol-*O*-methyltransferase (COMT)
Target Category:	Transporter binding, storage in sympathetic nervous system (SNS)
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No



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

Background

[PubMed]

R-(–)-[^{11}C]Epinephrine ([^{11}C]EPI) is a radioligand developed for positron emission tomography (PET) imaging of the sympathetic nervous system (SNS) (1, 2, 11). It is a catecholamine analog labeled with ^{11}C, a positron emitter with a physical half-life ($t_{½}$) of 20.4 min.

Many diseases affect the SNS, and imaging of 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 and subtypes of adrenergic receptors, and they are characterized as α_{1a} to α_{1c}, α_{2a} to α_{2c}, and β_1 to β_3 (6). All of the NE receptors belong to the G-protein-linked receptor superfamily and mediate slow neuromodulatory postsynaptic responses. 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 (7). 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 (8).

Molecular probes with structures closely related to NE can be used to assess the integrity of presynaptic sympathetic nerve terminals in various diseases. *In vivo* NE synthesis is similar to dopamine synthesis, and dopamine is converted to NE by the enzyme dopamine-β-hydroxylase (6). [^{123}I]-*meta*-Iodobenzylguanidine ([^{123}I]MIBG), a single-photon emission tomography (SPECT) agent, has been developed and used for neuronal

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imaging (9). 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 [^{123}I]MIBG. EPI is a *N*-methyl derivative of (–)-norepinephrine and is produced *in vivo* together with NE by the adrenal medulla and other chromaffin tissues (6, 9, 10). EPI is handled *in vivo* in a manner similar to that for NE, with binding to NET and transport by vesicular monoamine transporter into neuronal vesicles for storage. EPI is subject to metabolism by both monoamine oxidase and catechol-*O*-methyltransferase. Langer and Halldin (9) have reviewed and compared various PET and SPECT tracers for mapping the cardiac nervous system.

Synthesis

[PubMed]

Soussain et al (1) first synthesized [^{11}C]EPI by enzyme-catalyzed methylation. In that procedure, the [^{11}C]methyl group was sequentially transferred from L-[methyl-^{11}C]methionine to *R*-(–)-NE via *S*-adenosyl-L-[*methyl*-^{11}C]methionine by the enzyme phenylethanolamine-*N*-methyl transferase. L-[methyl-^{11}C]Methionine was first obtained by methylation of L-homocysteine thiolactone in a basic solution with [^{11}C]methyl iodide in acetone. The reaction was completed in 28-31 min. L-[methyl-^{11}C]Methionine was then enzymatically converted by L-methionine-*S*-adenosine transferase with adenosine triphosphate to *S*-adenosyl-L-[*methyl*-^{11}C]methionine. This step was done by incubating the mixture for 12 min at 40 °C. The final yield was reported to be 20% (55.5 MBq (1.5 mCi) at 65 min at the end of bombardment (EOB)) in 30-35 min from [^{11}C]methionine. The specific activity was 6.29 GBq (0.17 Ci)/µmol.

Chakraborty et al. (11) used a direct methylation method based on the fact that the parent amine was present in large excess, which minimized the probability of polymethylation. *R*-(–)-NE hydrochloride obtained commercially was first converted to free base by reaction with tetrabutylammonium hydrochloride under oxygen-free conditions. Either [^{11}C]methyl iodide or [^{11}C]methyl triflate was used as the radiomethylating agent. Free *R*-(–)-NE base was reacted with the methylating agent in dimethylformamide/dimethyl sulfoxide (3/1) and heated at 85 °C for 5 min. The product was purified by cation-exchange high-performance liquid chromatography. With [^{11}C]methyl iodide, the radiochemical yield was 5-10% at the EOB in a synthesis time of 35-40 min. The specific activity was 37-74 GBq (1-2 Ci)/µmol. When [^{11}C]methyl triflate was used, the yield was improved to 15-25% at the EOB with a specific activity of 33.3-81.4 GBq (0.9-2.2 Ci)/µmol

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Soussain et al. (1) performed a specific binding study of [^{11}C]EPI prepared by the enzymatic method in rat liver plasma membranes and found that the dissociation constant (K_D) was 54 nM, as determined by Scatchard plot. The capacity of specific

binding sites (B_{max}) was 412 fmol/mg. In comparison, (–)-^{3}H-NE had a K_D of 130 ± 60 nM and B_{max} of 340 ± 70 fmol/mg.

Nguyen et al. (12) conducted a myocardial kinetic study of [^{11}C]EPI in an isolated working rat heart model. [^{11}C]EPI was obtained with a specific activity of 18.5-37 GBq (0.5-1 Ci)/μmol and radiochemical purity >95%. All hearts were perfused with 11.1-16.7 MBq (300-450 μCi)/liter [^{11}C]EPI in a buffer for 20 min followed by 20 min of wash-out. There were no significant differences in the hemodynamic data (heart rate, pressure, coronary flow, and cardiac output) between the treated group and the untreated control group. [^{11}C]EPI had linear wash-in kinetics with K_i = 0.596 ± 0.198 ml/g/min and monoexponential wash-out kinetics with a clearance rate constant (k_2) of 0.00121 ± 0.00114 min^{-1}. The study indicated that the slow clearance during wash-out represented avid retention of [^{11}C]EPI in the myocardium. The study also indicated that 61% of ^{11}C]EPI was metabolized and released. [^{11}C]EPI radioactivity uptake and retention was decreased by treatment with 50 nM desipramine (DMI), an uptake-1 inhibitor, for both the wash-in and wash-out periods. When DMI was added to the wash-out period only, no effect was observed, indicating that the retention was independent of uptake-1 activity. Treatment with reserpine (vesicular blocker) decreased the K_i to 0.034 ± 0.010 ml/g/min and increased k_2 to 31.02 ± 10.88 min^{-1}.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

Soussain et al. (1) injected 8.14 MBq (0.22 mCi) of enzyme-prepared [^{11}C]EPI into a rabbit and studied the tissue distribution by gamma imaging and blood kinetics by serial blood samples. The images showed that the distribution was mainly in the heart, liver-pancreas, kidneys, suprarenal glands, and urinary bladder. The brain was not imaged. The blood kinetic study estimated that the global biologic $t_{½}$ in the circulating blood was 3 min.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Munch et al. (2) evaluated [^{11}C]EPI and [^{11}C]*meta*-hydroxyephedrine ([^{11}C]mHED) in 7 healthy volunteers and in 10 patients who had undergone heart transplantation within the previous 3.5-48 months. The specific activity, radiochemical purity, and chemical purity of the [^{11}C]EPI used were 33.3-74 GBq (0.9-2 Ci)/μmol, 98%, and 97%, respectively. The volunteers and patients received [^{11}C]EPI doses of 466.2 ± 29.6 MBq (12.6 ± 0.8 mCi) and 514.3 ± 44.4 MBq (13.9 ± 1.2 mCi), respectively. Blood sample analysis showed that [^{11}C]EPI was rapidly metabolized in both volunteers and patients. Unmetabolized [^{11}C]EPI in the blood was 65% at 5 min and decreased to <20% and 14% after 20 and 60 min, respectively. Clearance of activity from the myocardium was much slower; the myocardium clearance $t_{½}$ was 10.5 ± 3.2 h in healthy volunteers and 4.0 ± 1.1 in transplant patients. In comparison, the myocardium clearance $t_{½}$ of [^{11}C]mHED was 4.3 ± 2.4 and 1.5 ± 0.2 h, respectively. Images showed high myocardial uptake of [^{11}C]EPI radioactivity in volunteers and greatly reduced activity (up to 80% in denervated areas) in transplant patients. At 35 min in volunteers, the metabolite-corrected mean myocardial retention for [^{11}C]EPI was significantly greater than for [^{11}C]mHED (0.295 ± 0.022 min^{-1} *versus* 0.142 ± 0.012 min^{-1}; $P < 0.0001$). These values were significantly lower ($P < 0.0001$) in transplant patients: 0.055 ± 0.004 min^{-1} and 0.050 ± 0.006 min^{-1} for [^{11}C]EPI and [^{11}C]mHED, respectively.

NIH Support

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