P^2,P^3-[^{18}F]Monofluoromethylene diadenosine-5′,5‴-P^1,P^4-tetraphosphate

[^{18}F]AppCHFppA

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Chemical name:	P^2, P^3-[^{18}F]Monofluoromethylene diadenosine-5',5'''-P^1,P^4-tetraphosphate	
Abbreviated name:	[^{18}F]AppCHFppA	
Synonym:		
Agent category:	Small molecule	
Target:	Adenosine nucleotide receptor	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal/contrast:	^{18}F	
Activation:	No	
Studies:	• Rodents • Non-primate non-rodent mammals	No structure is currently available in PubChem.

Background

[PubMed]

Extracellular adenine 5'-diphosphates (ADP) are released from a variety of cells and regulate many physiological processes by interacting with purine receptors or adenosine receptors (1). In particular, high concentrations of ADP are built up in atherosclerotic lesions, where they either inhibit platelet aggregation *via* binding to platelet receptors (P2T) and/or accumulate in macrophages, monocytes, and smooth muscle cells *via* binding to purine receptors (P2X and P2Y) (2, 3). Diadenosine oligophosphate (Ap4A), a

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nucleotide oligomer made from two adenosine moieties joined in 5'-5' linkage by a tetraphosphodiester linkage (4), is a competitive inhibitor of ADP in platelet aggregation (5, 6). Because platelet aggregation plays a central role in arterial thrombosis and plaque formation, Ap4A was initially proposed as a therapeutic agent for inhibition and treatment of plaque formation (1). However, Ap4A has a short blood half-life due to the rapid degradation by phosphodiesterase (5). A series of analogs are synthesized by substituting the oxygen bridge in the β,β' position of Ap4A with -CHX- to produce β,β'-monohalomethylene diadenosine 5',5'''-P^1,P^4-tetraphosphate (AppCHXppA, X=Cl, F) (6). This modification increases its resistance to hydrolytic enzymes and generates a potent antithrombotic agent (6). For instance, AppCHFppA can effectively inhibit ADP-induced platelet aggregation with a 4 μM of half maximal (50%) inhibitory concentration (5).

[^{18}F]AppCHFppA is an ^{18}F-labeled molecular probe for positron emission tomography (PET) (7). ^{18}F has a half-life of 109.8 min, an ideal radionuclide for routine PET imaging (8). The low β^+ energy of ^{18}F provides a short positron linear range in tissues and particularly high resolution in PET imaging (8). [^{18}F]AppCHFppA can accumulate selectively in atherosclerotic lesions, which allows noninvasive characterization of plaque inflammation with PET imaging (7).

Synthesis

[PubMed]

[^{18}F]AppCHFppA was obtained through a multi-step synthesis (7). First, the precursor AppCHClppA was produced by condensation of AMP, dAMP, ADP, and deoxyadenosine 5'-thiophosphate with monochloromethylene or bismonochloromethylene triphosphonate in the presence of diphenyl phosphochloridate (9). AppCHClppA was converted to tributylammonium salts, which dissolve in organic solvents, and then it was reacted with [^{18}F]fluoride (3.7 GBq (100 mCi)) by nucleophilic substitution (7). The produced [^{18}F]AppCHFppA had a yield of 20–40% and a radiochemical purity of 98% (specific activity >185,000 GBq/mmol (5,000 Ci/mmol)) for injection.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

Elmaleh et al. performed a biodistribution study of [^{18}F]AppCHFppA in rats (300–350 g) (7). After administration of [^{18}F]AppCHFppA (185 MBq/kg body weight), animals were

euthanized. Tissue samples were collected, and radioactivity was measured with a gamma counter. [^{18}F]AppCHFppA exhibited typical ADP behavior in normal rats and had significant myocardial uptake and fast kidney clearance. The accumulation (percentage of injected dose per gram (% ID/g)) in most tissues was measured at 5, 30, and 60 min: blood (0.78, 0.16, and 0.07), heart (0.33, 0.08, and 0.03), lung (0.62, 0.18, and 0.08), liver (0.33, 0.08, and 0.03), and kidney (2.10, 0.90, and 0.03). Bone demonstrated some accumulation (1.04, 1.51, and 1.83) as a result of defluorination and/or tetraphosphonate bone uptake. Of all the tissue samples, the kidney contained the highest early concentration of tracer, the liver and lung had higher concentrations than the spleen and muscle, and the spleen accumulation was similar to that in muscle. No metabolized rate was reported for AppCHFppA.

Other Non-Primate Mammals

[PubMed]

Elmaleh et al. used [^{18}F]AppCHFppA to examine atherosclerotic lesions in rabbits (2.5–3.0 kg) (7). After induction injury to the aorta, the rabbits were maintained on a high-cholesterol diet for 3–6 months to achieve atherosclerosis and inflammation. MicroPET imaging was performed after intravenous injection of [^{18}F]AppCHFppA (118 MBq). The images demonstrated a rapid accumulation of [^{18}F]AppCHFppA in the atherosclerotic abdominal aorta. The atherosclerotic lesions were clearly visible 10 min after injection and retained through the 1-h imaging session. During the imaging study, blood was sampled at 1–40 min to evaluate blood clearance of [^{18}F]AppCHFppA. The lesion/blood radioactivity ratio was >5:1 at 1 h. After the imaging experiment, small sections were extracted from both lesional and normal aortic segments (aortic and iliac specimens) for histological examination. The [^{18}F]AppCHFppA uptake measured by PET was well correlated with the immunostaining of plaque macrophage density.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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