8-Cyclopentyl-3-(3-[^{18}F]fluoropropyl)-1-propylxanthine

[^{18}F]CPFPX

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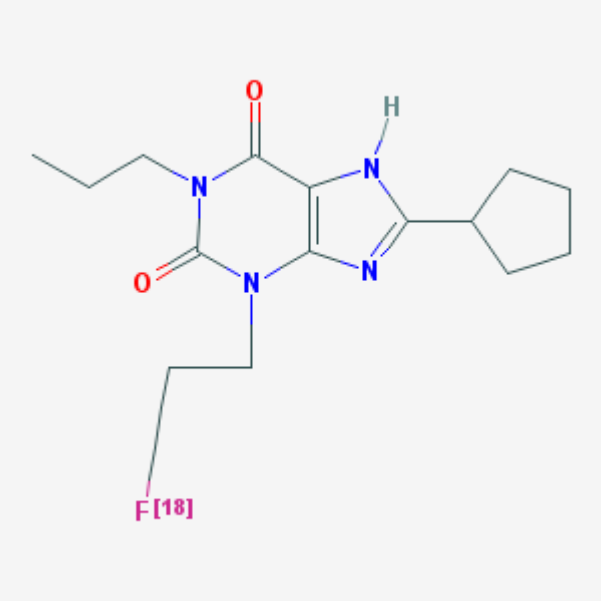
Chemical name:	8-Cyclopentyl-3-(3-[^{18}F]fluoropropyl)-1-propylxanthine
Abbreviated name:	[^{18}F]CPFPX
Synonym:	
Agent category:	Compound
Target:	Adenosine A_1 receptor
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

Adenosine is an endogenous nucleoside, which modulates a number of physiological functions in the central nervous system (CNS) and in peripheral organs, such as the heart, kidney and muscle (1, 2). The effect is mediated by two major subtypes of receptors (A_1 and A_{2A} receptors) and two minor subtypes (A_{2B} and A_3). In the CNS, A_1 receptors are present both pre- and postsynaptically in the hippocampus, cerebral cortex, thalamus, striatum, and cerebellum. A_{2A} receptors are highly concentrated and co-localized with dopamine D_1 and D_2 receptors in the striatum, nucleus accumbens, and olfactory tubercle. A_{2A} receptors are also present in the hippocampus and cortex. A_{2B} receptors are widely distributed but high in gastrointestinal tract. A_3 receptors are also widely distributed but high in testis. A_1 and A_3 receptors mediate inhibition of adenylyl cyclase, whereas A_{2A} and A_{2B} receptors mediate stimulation. Changes in the adenosine functions are implicated in epilepsy, ischemic cerebral stroke, movement disorders, sleep disorders and psychiatric disorders (3-5).

A_1 receptors have been studied *in vivo* by positron emission tomography (PET) using [1-methyl-^{11}C]8-dicyclopropylmethyl-1-methyl-3-propylxanthine ([18F]CPFPX), a methyl xanthine analog of KF15372 with selective A_1 antagonistic activity (6). 8-Cyclopentyl-1,3-dipropylxanthine was reported to be a selective A1 receptor antagonist and its analog, 8-Cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine (CPFPX) has been labeled with ^{18}F as 8-Cyclopentyl-3-(3-[^{18}F]fluoropropyl)-1-propylxanthine ([^{18}F]CPFPX). [^{18}F]CPFPX is being developed as a PET agent for the non-invasive study of the human brain.

Synthesis

[PubMed]

In the report by Noguchi et al., [18F]CPFPX was synthesized by alkylation of the 1-N-desmethyl precursor (8-dicyclopropylmethyl-3-propylxanthine) with [^{11}C]methyl iodide in the presence of NaH, with subsequent purification by high-performance liquid chromatography. Radiochemical purity was greater than 98%. The average specific activity was 49 GBq/μmol (1.3 Ci/μmol) at the end of synthesis. Total synthesis time was 45-60 min.

Kawamura et al. described the synthesis of [^{18}F]CPFPX from the desmethyl precursor with [^{11}C]methyl triflate in the presence of Cs_2CO_3 providing an improved radiochemical yield of 55.3% based on [^{11}C]methyl triflate. No time of synthesis and specific activity were reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The K_i values of MPDX and KF15372 for the A_1 receptors were 4.2 nM and 3.0 nM, respectively. The K_i values for both antagonists for A_{2A} receptors were >100 nM.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal mice showed high accumulation of radioactivity in the liver (8.5% injected dose (ID)/g), followed by the small intestine (3.8% ID/g), pancreas (3.2% ID/g), kidney (2.3% ID/g), and spleen (1.9% ID/g) at 30 min after injection of [18F]CPFPX . The level of radioactivity was low in the brain (0.7% ID/g) and blood (1.5% ID/g). Coadiministration of the A_1 antagonist KF15372 but not A_{2A} antagonist KF17837 decreased the accumulation in the brain in a dose-dependent manner at 15 min post injection. About 22-27% and 62-65% of radioactivity in the plasma and cerebral cortex was intact [18F]CPFPXat 30 min post injection, respectively.

Kiyosawa et al. studied the changes in the distribution of central benzodiazepine and presynaptic A_1 receptors in the superior colliculus (SC) and visual cortex (VC) of rats following monocular enucleation. The uptake of [^{14}C]deoxyglucose in the SC was depressed immediately after enucleation and gradually recovered. The binding of [^{11}C]flumazenil to central benzodiazepine receptors in the contralateral SC was increased at week 2, and then returned to the pre-enucleation levels. The uptake of [18F]CPFPXby the A_1 receptors in the contralateral SC decreased by about 67% on day 5 after enucleation and remained low thereafter. In the contralateral VC, the uptake of [^{14}C]deoxyglucose decreased immediately after the enucleation followed by a gradual recovery, whereas the uptake of [^{11}C]flumazenil and [18F]CPFPXwas not affected. The axon degeneration decreased the A_1 receptor density and resulted in a transient increase of postsynaptic central benzodiazepine receptor density in the enucleated rats.

Other Non-Primate Mammals

[PubMed]

Shimadaet al. obtained PET images of the brain in cats after injection of 199 MBq (5.4 mCi) [18F]CPFPX . Regional brain distribution and kinetics of [18F]CPFPXwere studied with MRI co-registration. The cerebral cortex exhibited the highest accumulation of [18F]CPFPX(distribution volume, DV = 4.2 ± 1.7) followed by the striatum (DV = 3.8 ± 1.3), cerebellum (DV = 3.5 ± 1.2), thalamus (DV = 3.1 ± 1.2), midbrain (DV = 2.6 ± 0.9) and whole brain (DV = 2.4 ± 0.8). Co-injection with unlabeled MDPX inhibit binding of [18F]CPFPXto the regional brain areas.

Nariai et al. studied the adenosine A_1 receptor with PET using [18F]CPFPXin a cat cerebral ischemic model (middle cerebral artery occlusion and reperfusion). Eighteen adult cats underwent PET measurement of cerebral blood flow (CBF) with ^{15}O-labeled

water, A_1 receptors with [18F]CPFPX , central benzodiazepine receptors with [^{11}C]flumazenil and glucose metabolism with [^{18}F]fluorodeoxyglucose (FDG) after 60 min occlusion. [18F]CPFPXbinding and [^{11}C]flumazenil binding, but not CBF and FDG uptake, were significantly reduced in the groups with severer ischemic insult than in the groups with no or milder insults. Of the two receptor ligands, the reduction rate of the [18F]CPFPXbinding to A_1 receptors was larger in a group that caused fatal ischemic insult. Therefore, [18F]CPFPXPET imaging was suitable in evaluating the function of adenosine A_1 receptors in relation to cerebral ischemia.

Non-Human Primates

[PubMed]

Using PET, Ishiwata et al. obtained serial brain scans in 2 monkeys after injection of 91-141 MBq (2.5-3.8 mCi) [18F]CPFPX . The accumulation of radioactivity in the brain peaked at 5 min, and then decreased for the final 60 min of study. The fraction of unchanged [18F]CPFPXin blood samples determined by HPLC was 78%, 70%, 54% and 41% at 5, 15, 30 and 60 min, respectively.

Human Studies

[PubMed]

Kimura et al. reported on PET studies in 7 healthy volunteers after injection of 259-777 MBq (7-21 mCi) of [18F]CPFPX . Using Logan plot analysis, the striatum (0.55) exhibited the highest binding potential (BP, cerebellum as a reference) for [18F]CPFPX , followed by thalamus (0.50), occipital cortex (0.40), parietal cortex (0.33) and temporal cortex (0.28). Fukumitsu et al. extended the human PET studies using Logan plot analysis with arterial input. The DV was large in the striatum and thalamus, moderate in the cerebral cortices and small in the cerebellum. The distribution of pattern of [18F]CPFPXin the brain was discretely different from that of CBF as measured by ^{15}O-labeled water. At 60 min after injection of [18F]CPFPX , 75% of radioactivity was in the intact tracer. This percentage was much higher than those in rats (22-27%), cats (6.5%) and monkeys (41%). Naganawa et al. reported that DV and BP could be accurately estimated without arterial blood sampling in 25 subjects. Internal dosimetry data for [18F]CPFPXin humans are not available in the literature.

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