6-*O*-(2-[^{18}F]Fluoroethyl)-6-*O*-desmethyldiprenorphine

[^{18}F]FDPN

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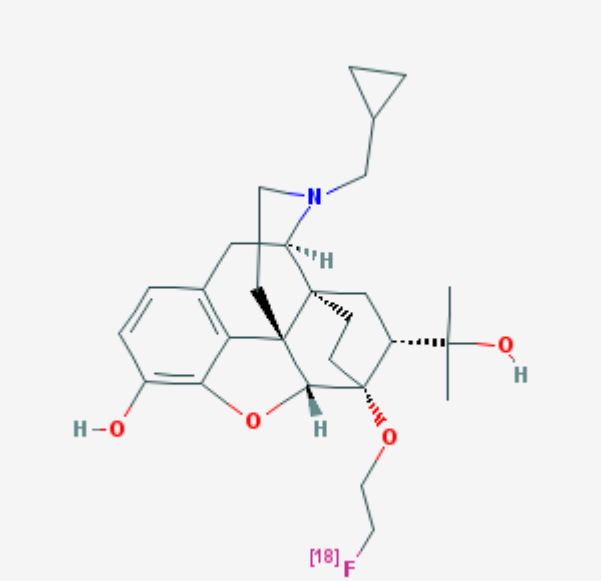
Chemical name:	6-*O*-(2-[^{18}F]Fluoroethyl)-6-*O*-desmethyldiprenorphine
Abbreviated name:	[^{18}F]FDPN
Synonym:	
Agent Category:	Compound
Target:	Opioid receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

Opioids such as morphine are analgesics commonly used in clinical practice. Three opioid receptors (mu, μ; delta, δ; and kappa, κ) that mediate opioid effects have been identified by molecular cloning: δ (enkephalin-preferring), κ (dynorphin-preferring), and μ (ß-endorphin-preferring) (1). Pharmacological studies suggest that each type of opioid receptor consists of subtypes of receptors (2, 3). Their specificity and ubiquitous location are present in both the central and peripheral nervous system. The opioid receptors (G-protein-coupled, resulting in decrease in adenylyl cyclase activity) play an important role in the regulation of analgesia, shock, appetite, thermoregulation, and cardiovascular, mental and endocrine function (2-5). Although the μ opioid receptor is the major receptor to mediate the analgesic effects of opioids, δ and κ receptors are also important in antinociception. Opioids have been found to protect cells from ischemic injury in the heart and brain via the δ receptors. On the other hand, κ antagonists prevent neurodegeneration.

In humans, the κ opioid receptors (κ_1 and κ_2) are the most abundant brain opioid receptors and are widely distributed in deeper layers of the neocortex (particularly the temporal, parietal, and frontal cortices), striatum, and thalamus, with lower levels in the amygdala, hippocampus, occipital cortex, and cerebellum (6-8). The κ opioid receptors have been implicated in several clinical brain disorders, including drug abuse (9), epilepsy (10), Tourette's syndrome (11), and Alzheimer's disease (12).

Diprenorphine is a highly potent and nonselective opioid receptors antagonist with subnanomolar affinity (13). Diprenorphine has been labeled as [6-*O*-*methyl*-^{11}C]diprenorphine ([^{11}C]DPN) (14, 15). [^{11}C]DPN is being developed as a positron emission tomography (PET) agent for the non-invasive study of opioid receptors in the brain. However, [^{11}C]DPN PET studies are complicated by the 20.4 min short half-life ($t_{1/2}$) of ^{11}C. 6-*O*-(2-[^{18}F]Fluoroethyl)-6-*O*-desmethyldiprenorphine ([^{18}F]FDPN) has been synthesized as a ^{18}F ($t_{1/2}$ = 110 min) labeled analog of DPN to improve signal intensity, accuracy, and sensitivity of PET studies of opioid receptors in the brain.

Synthesis

[PubMed]

Wester et al. (16) reported synthesis of [^{18}F]FDPN by a 3-step reaction, which consisted of ^{18}F-fluorination of ethylene glycol-1,2-ditosylate, ^{18}F-fluoroethylation of [3-O-trityl-6-O-desmethyl]diprenorphine, and final acidic deprotection of the product. An average radiochemical yield was 22 ± 7% with a total synthesis time of 100 min. An average specific activity was 37 GBq/μmol (1 Ci/μmol at end of synthesis) with a radiochemical purity of >98%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Chang et al. (17) reported that [^{3}H]DPN had a K_d of 0.23 nM and a B_{max} of 530 fmol/mg protein *in vitro* binding assays using rat brain membranes. DPN had K_i values of 0.20, 0.18, and 0.47 nM for the μ, δ, and κ opioid receptors, respectively. Therefore, DPN binds to all three subtypes of opioid receptors equally with good affinity.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in female mice injected with 185 MBq (5 mCi) [^{18}F]FDPN were performed by Wester et al. (16) showing high accumulation of radioactivity in the brain (4.36 ± 0.49% injected dose (ID) at 5 min post injection) as compared with [^{11}C]DPN (7.5 ± 0.89%ID/g). The bulk of accumulation was in the lungs, liver, intestine, and kidneys at 5 min. Clearance of radioactivity occurred at 240 min for all tissues except the bone and intestine, which showed an increase from 0.82%ID/g at 60 min to 1.51%ID/g at 240 min and from 10.3%ID/g at 5 min to 36.85%ID/g at 240 min, respectively. Hence, there is a small trapping of free ^{18}F-fluoride in the bone and most of the [^{18}F]FDPN is hepatobiliary excreted. The fraction of unchanged [^{18}F]FDPN in the brain determined by HPLC was >80% at 30 min after injection. The fraction of unchanged [^{18}F]FDPN in plasma samples determined by HPLC was 5% at 30 min after injection with one major hydrophilic metabolite. *Ex vivo* autoradiographic studies of rat brain at 60 min after injection of 0.0185 MBq (0.5 μCi) [^{18}F]FDPN revealed radioactivity in the cerebral cortex, cerebellum, striatum, and thalamus. Pretreatment with 1 mg/kg naloxone blocked the radioactivity to the same level as the cerebellum.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Wester et al. (16) studied one adult male volunteer with [^{18}F]FDPN PET imaging over a period of 90 min. The clearance of the tracer from plasma to tissue from spectral analyses was calculated from the impulse response function at 60 min (IRF_{60}, highly correlated with distribution volume) using the arterial input function. High levels of [^{18}F]FDPN radioactivity were found in the striatum (IRF_{60} = 0.16101 ± 0.03251), thalamus (IRF_{60} = 0.16839 ± 0.04668), and medial prefrontal cortex (IRF_{60} = 0.16563 ± 0.14703). Low levels were found in the occipital cortex (IRF_{60} = 0.03056 ± 0.01123). The [^{18}F]FDPN binding pattern was similar to that of a control group of nine healthy volunteers after injection of [^{11}C]DPN. The fraction of unchanged [^{18}F]FDPN in plasma samples determined by HPLC was 50% at 15 min after injection.

Spilker et al. (18) evaluated [^{18}F]FDPN kinetics in the human brain with compartmental and non-compartmental modeling approaches. The results indicate that a two-tissue compartmental model best characterizes the data obtained following a bolus injection of [^{18}F]FDPN (120-min scanning protocol). Estimates of distribution volume (DV) were robust, being highly correlated for the one-tissue compartmental model as well as the Logan model and the basis function method. The binding potential (BP) values showed more variability between methods. BP values were also found to correlate with DV values. Furthermore, the DV estimates were also stable under a shortened protocol of 60 min, showing a significant correlation with the full protocol. However, Boecker et al. (19) concluded from their studies that [^{18}F]FDPN PET should be sampled not to be shorter than 90 min.

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