[6-*O*-*methyl*-^{11}C]Diprenorphine

[^{11}C]DPN

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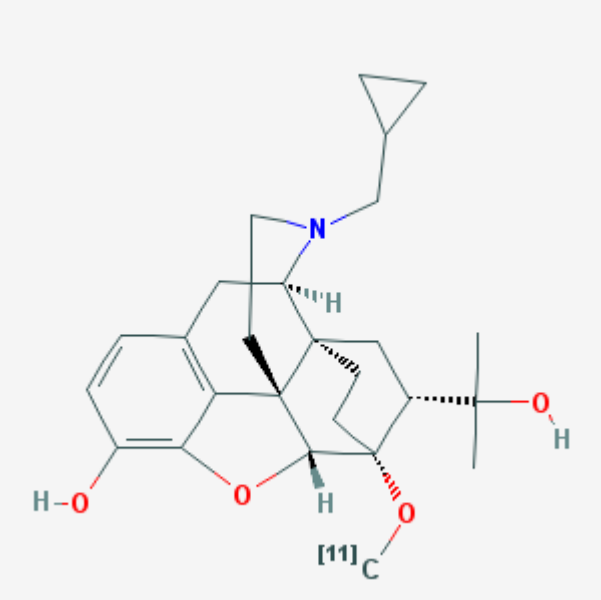
Chemical name:	[6-*O*-*methyl*-^{11}C]Diprenorphine
Abbreviated name:	[^{11}C]DPN
Synonym:	[^{11}C]Diprenorphine
Agent category:	Compound
Target:	Opioid receptors
Target category:	Receptor
Method of detection:	PET
Source of signal \contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

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Opioids such as morphine are commonly used analgesics 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 (morphine and ß-endorphin-preferring) (1). Each type of opioid receptors consists of subtypes of receptors as suggested by pharmacological studies (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, cardiovascular, mental and endocrine function (2-5). Although μ opioid receptors are 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 ischemia injury in the heart and brain via the δ receptors. On the other hand, κ antagonist prevents neurodegeneration.

The μ opioid receptors are localized predominately in the hypothalamus and thalamus, and the δ opioid receptors are localized predominately in the striatum, limbic system, and cerebral cortex (6, 7). 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 temporal, parietal, and frontal cortices), striatum, amygdala, and thalamus, with lower levels in the hippocampus, occipital cortex, and cerebellum (8-10). The κ opioid receptors have been implicated in several clinical brain disorders, including drug abuse (11), epilepsy (12), Tourette's syndrome (13), and Alzheimer's disease (14).

Diprenorphine is a highly potent and nonselective opioid receptors antagonist with subnanomolar affinity (7). Diprenorphine has been labeled as [6-*O*-*methyl*-^{11}C]diprenorphine ([^{11}C]DPN) (15, 16). [^{11}C]DPN is being developed as a PET agent for the non-invasive study of opioid receptors in the brain.

Synthesis

[PubMed]

Lever et al. (15) reported synthesis of [6-*O*-methyl-^{11}C]diprenorphine by [^{11}C]-*O*-methylation of 3-O-*t*-butyldimethylsilyl-(6-*O*-desmethyl)diprenorphine with [^{11}C]methyl iodide , and final acidic deprotection of the product. An average radiochemical yield was 10% with a total synthesis time of 30 min. An average specific activity was 64 GBq/μmol (1.74 Ci/μmol at end of synthesis) with a radiochemical purity of >98%.

Luthra et al. (16) reported an automated radiosynthesis of [6-*O*-methyl-^{11}C]diprenorphine by

O-methylation of (3-*O*-trityl,6-desmethyl)diprenorphine with [^{11}C]iodomethane in the presence of NaH in DMF, following by de-protection acid hydrolysis. The two-step reaction provided [^{11}C]DPN in a 13–19% radiochemical yield with a specific activity of 15.5–23.8 GBq/μmol (0.41-0.64 Ci/μmol) at end of synthesis. The preparation takes 45 min from end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Chang et al. (6) 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 rats injected with 18.5 MBq (0.5 mCi) [^{11}C]DPN were performed by Rajeswaran et al. (17) showing high accumulation of radioactivity in the thalamus and caudate putamen at 40 min post injection. Brain region to cerebellum ratios increased over time with ratios at 40 min of 8.6 and 7.2 for the thalamus and caudate putamen, respectively. Pretreatment with naloxone (an opioid receptor competitive antagonist) decreased both ratios to ~2. The cerebellum had low activity because of more rapid washout. Naloxone also blocked the cerebellum uptake from 0.26 to 0.14, indicating there are a few opioid receptors. The accumulation of radioactivity in the striatum and cerebellum and their blocking with DPN (200 ng/kg) and naloxone (1 mg/kg) pretreatment were confirmed by PET imaging in another experiment.

Shiue et al. (18) demonstrated a high accumulation of [^{11}C]DPN in the mouse brain (1.2% injected dose) at 30 min after injection. The fraction of unchanged [^{11}C]DPN in the brain determined by HPLC was 82-89% at 30 min after injection.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Shiue et al. (18) studied two adult female baboons with [^{11}C]DPN PET imaging under baseline conditions and after pretreatment with naloxone (1 mg/kg). Four parameter constants (k_1-k_4) were derived from PET scan data using Logan analysis with arterial input function. The three regions of interest were the striatum, thalamus, and cerebellum. High levels of [^{11}C]DPN radioactivity were found in all three regions initially. However, the radioactivity in the cerebellum was washed out faster than the striatum and thalamus. The striatum/cerebellum ratio was 3.2 at 90 min. Pretreatment with naloxone blocked the

accumulation of [^{11}C]DPN radioactivity in the striatum and thalamus more significantly than in the cerebellum. The fraction of unchanged [^{11}C]DPN in plasma samples determined by HPLC was 63% at 20 min and 28% at 60 min after injection.

Human Studies

[PubMed]

Sadzot et al. (19) reported PET studies in human brain using high and low specific activity [^{11}C]DPN. Non-steady-state three-compartment modeling and non-linear least-squares curve fitting were performed to obtain in vivo estimates of B_{max} and K_d in eight brain regions. The B_{max} values were from 2.3 ± 0.5, 6.8 ± 2.1, 12.0 ± 3.7, 13.1 ± 3.6, 13.4 ± 2.6, 18.6 ± 1.9, 19.9 ± 10.0, 20.5 ± 7.3 nM in the occipital cortex, cerebellum, parietal cortex, frontal cortex, temporal cortex, thalamus, caudate, and cingulated cortex, respectively. The averaged K_d from the eight brain regions was 0.85 ± 0.17 nM. Binding potentials and volumes of distribution can also be estimated using only high specific activity [^{11}C]DPN and the occipital cortex as a reference region. Pretreatment with 1 mg/kg naloxone, the uptake of [^{11}C]DPN was reduced to background levels throughout the brain.

Jones et al. (20, 21) performed [^{11}C]DPN PET studies endogenous opiate response to pain (in and out of pain) in patients with rheumatoid arthritis (n = 4). There were significant increases in [^{11}C]DPN binding in association with a reduction in pain in most of the areas of the brain that were sampled apart from the occipital cortex, such as in the frontal cortex, cingulate cortex, temporal cortex, and straight gyrus. Jones et al. (22) and Willoch et al. (23) also found there were decreases in [^{11}C]DPN binding in various cerebral cortices and the thalamus in patients with poststroke pain. These findings suggest that there are substantial increases in opioid receptor occupancy by endogenous opioid peptides during pain.

Weeks et al. (24) compared regions of interest (ROIs) analytical approaches with statistical parametric mapping (SPM) of [^{11}C]DPN PET findings in five patients with Huntington's disease (HD) and nine age-matched controls. The ROIs were placed on the caudate, putamen and occipital reference. Ratios of striatal-occipital uptake from averaged static images centered at 60 minutes showed an average of 20% reduction of [^{11}C]DPN receptor binding in the caudate ($P = 0.034$) and 15% reduction in the putamen ($P = 0.095$) in the HD patients. Studies performed with SPM revealed symmetrical [^{11}C]DPN binding decreases in the caudate (peak 40% decrease) and putamen (peak 24% decrease) with also decreases in the cingulated (peak 48% decrease), prefrontal (peak 13% decrease), and thalamic (peak 19% decrease) regions. Using these two approaches, Piccini et al. (25) found significantly reduction of [^{11}C]DPN opioid binding in the striatum and thalamus in levodopa-induced dyskinetic, but not in nondyskinetic, Parkinson's disease (PD) patients by using the ROI approach. The SPM approach confirmed reduced availability in these areas and, in addition, showed decreased cingulate and increased prefrontal opioid receptor binding in the dyskinetic PD patients. Burn et al. (26) has reported previously

that there were no significant decreases in [^{11}C]DPN binding in the caudate and putamen of eight PD patients compared with eight normal controls.

Mayberg et al. (27) reported that [^{11}C]DPN binding was not significantly different among regions in the focus and nonfocus temporal lobes in eleven patients with epilepsy. However, Koepp et al. (28) reported that [^{11}C]DPN binding to opioid receptors was significantly lower (P<0.05) in the left parieto-temporo-occipital cortex in five reading-epilepsy patients compared with six age-matched controls. Therefore, endogenous opioid peptides were released in localized areas of the brain during seizures induced by reading.

Internal dosimetry data for [^{11}C]DPN in humans are not available in the literature.

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