*N*1′-([^{11}C]Methyl)naltrindole

[^{11}C]MeNTI

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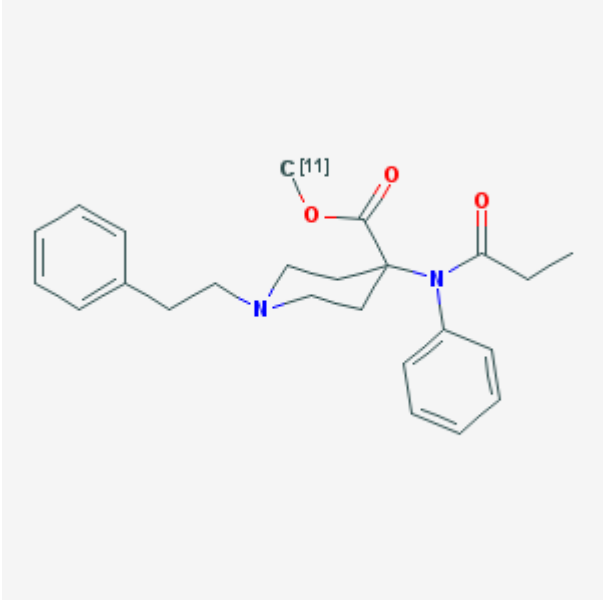
Chemical name:	*N*1'-([^{11}C]Methyl)naltrindole
Abbreviated name:	[^{11}C]MeNTI
Synonym:	
Agent category:	Compound
Target:	Delta (δ) opioid receptor
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

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

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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 μ opioid receptors have been implicated in several clinical brain disorders, including drug and alcohol abuses, epilepsy, and pain pathways.

Carfentanil (CFN) is a highly potent and selective μ opioid receptor agonist with subnanomolar affinity (K_d, 0.08 nM). [^{11}C]CFN is being developed as a positron emission tomography (PET) agent for the non-invasive studies of μ opioid receptors in the brain. On the other hand, *N*1'-methylnaltrindole (MeNTI) is a potent and selective δ opioid receptor antagonist (K_i, 0.02 nM). [^{11}C]MeNTI has been prepared for studying the role of δ opioid receptor in health and disease by PET imaging.

Related Resource Links:

- Chapters in MICAD (opioid receptors)
- Gene information in NCBI (μ opioid receptor, δ opioid receptor)
- Articles in Online Mendelian Inheritance in Man (OMIM) (μ opioid receptor, δ opioid receptor)
- Clinical trials (opioid receptors)
- Drug information in FDA (opioid receptors)

Synthesis

[PubMed]

Lever et al. (11) reported synthesis of [^{11}C]MeNTI by [^{11}C]-*N*-methylation of 3-*O*-benzylnaltrindole with [^{11}C]iodomethane, and final hydrogenolysis of the benzyl protecting group. An average radiochemical yield was 6% (based on [^{11}C]iodomethane) with a total synthesis time of 24 min from end of bombardment. An average specific activity was 76 GBq/μmol (2.05 Ci/μmol) at end of synthesis with a radiochemical purity of >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Portoghese et al. (12) reported that MeNTI had K_i values of 0.02, 14, and 65 nM for the δ, μ, and κ opioid receptors, respectively. Therefore, MeNTI exhibits excellent overall selectivity of 700-fold δ over μ receptors and >3200-fold δ over κ receptors.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in mice injected with 14.5 MBq (0.4 mCi) [^{11}C]MeNTI were performed by Lever et al. (11) showing high accumulation of radioactivity in the striatum, olfactory tubercles and cortex, followed by hippocampus, thalamus, hypothalamus and cerebellum at 15-90 min post injection. The regional accumulation correlated linearly with *in vitro* receptor binding in similar brain regions (r = 0.93). Pretreatment with naltrindole (a δ opioid receptor antagonist) decreased accumulation of radioactivity in the striatum, olfactory tubercles and cortex by 65-75% but not by cyprodime (a μ antagonist) and U50,488 (a κ agonist).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Madar et al. (13) reported PET studies in normal human brain (n = 4) using [^{11}C]MeNTI. [^{11}C]MeNTI accumulation was highest in regions of the neocortex (insular, parietal, frontal, cingulate, and occipital), caudate nucleus, and putamen. Binding was intermediate in the amygdala and lowest in the cerebellum and thalamus. Naltrexone pretreatment inhibited [^{11}C]MeNTI binding effectively in δ receptor-rich regions, and its inhibitory potency correlated well (r = 0.88) with the *in vitro* regional distribution of δ opioid sites from postmortem human brains.

Madar et al. (14) performed PET studies in patients (n = 10) with temporal lobe epilepsy. Paired measurements of δ and μ opioid receptor binding and metabolic activity were performed with PET using [^{11}C]MeNTI and [^{11}C]CFN and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), respectively. Binding of [^{11}C]MeNTI and [^{11}C]CFN increased and [^{18}F]FDG uptake decreased in the temporal cortex (TC) ipsilateral to the epileptic focus. Decreases in [^{18}F]FDG uptake were more widespread regionally than were increases in opioid receptors. Increases in μ receptor binding were confined to the middle region of the inferior TC, whereas binding of δ receptors increased in the mid-inferior TC and anterior region of the middle and superior TC.

Madar et al. (15) performed PET studies in patients (n = 7) with lung carcinoma. Elevated tumor binding of [^{11}C]MeNTI and [^{11}C]CFN was detected in all but one patient with a large necrotic center in the tumor. The mean [^{11}C]MeNTI tumor's standard uptake value (SUV) was 7.4 ± 0.85 compared with 1.8 ± 0.44 in the healthy lung tissue. [^{11}C]CFN binding in tumor was significantly (P = 0.003) lower than that of [^{11}C]MeNTI. The average [^{11}C]CFN SUVs in tumor and host lung were 2.7 ± 0.72 and 0.91 ± 0.25, respectively. The mean specific/nonspecific binding ratio was greater for [^{11}C]MeNTI (4.32 ± 1.30) than that for [^{11}C]CFN (2.42 ± 1.17). Naloxone treatment inhibited 50% and 44% of the specific/nonspecific binding ratios of [^{11}C]MeNTI and [^{11}C]CFN, respectively. The mean [^{18}F]FDG SUVs in tumor and host lung (n = 4) were 5.70 ± 1.29 and 0.66 ± 0.14, respectively.

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