m-Cyano-*p*-[^{18}F]fluorohippurate

[^{18}F]-CNPFH

Arvind Chopra, PhD[1]

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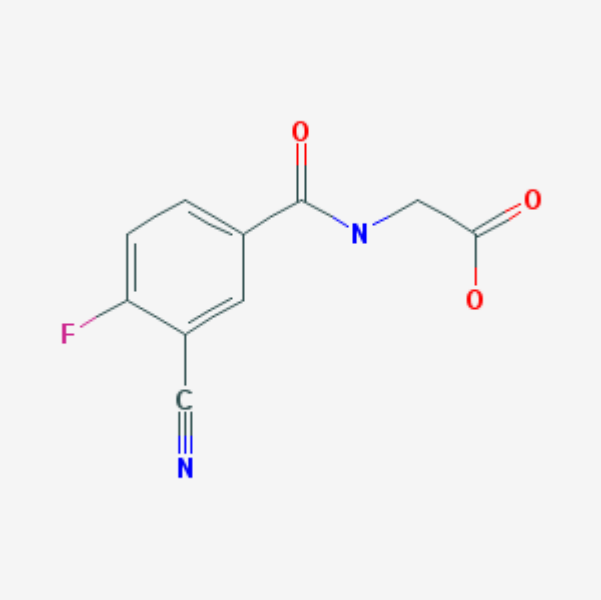
Chemical name:	*m*-Cyano-*p*-[^{18}F]fluorohippurate
Abbreviated name:	[^{18}F]-CNPFH
Synonym:	
Agent Category:	Compound
Target:	Organic anion transporter 1 (OAT1)
Target Category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Although *ortho*-[^{131}I]-iodohippurate ([^{131}I]-OIH) is considered a gold standard for renal plasma flow imaging and provides quantitative results with single-photon emission tomography (SPECT), images produced with this agent are not superior to those obtained

[1] National Center for Biotechnology Information, NLM, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

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with either ^{99m}Tc-labeled mercaptoacetylglycylglycylglycine ([^{99m}Tc]-MAG$_3$) which is secreted by the renal proximal tubules or ^{99m}Tc-labeled diethylenetriamine pentaacetic acid ([^{99m}Tc]-DTPA), which is filtered by the glomeruli (1). As a consequence, based on the superior imaging properties of ^{99m}Tc, [^{99m}Tc]-MAG$_3$ is often used with planar gamma imaging in the clinic to evaluate kidney function and perform renal scans (renography) (2). However, even with these radiolabeled compounds, a low signal/background ratio is obtained from the kidneys due to a differential attenuation of the ^{99m}Tc-gamma radiation between the two organs. In addition, the quantitative data generated with this tracer are of poor quality. Therefore, investigators are evaluating the use of dynamic SPECT or positron emission tomography (PET) to assess kidney function and/or renography because these modalities provide substantially superior quantitative results compared to planar imaging. PET offers several benefits over SPECT for renography because PET has higher spatial resolution and sensitivity, shows minimal differential signal attenuation between the kidneys, and can be used for real-time acquisition of the dynamic images (3). In an effort to develop an alternate tracer that can be used to evaluate kidney function and perform renography with PET, *para*-^{18}F-fluorohippurate ([^{18}F]-PFH), a renal tubular agent, was identified as a potential candidate by Awasthi et al. (3). The investigators hypothesized that [^{18}F]-PFH could be a superior PET renal imaging agent compared to [^{99m}Tc]-MAG$_3$ because of its pharmacokinetic and imaging characteristics. In a preliminary investigation, it was shown that [^{18}F]-PFH was suitable for renography in normal rats and that high-quality dynamic PET images could be obtained from the animals (3).

The synthesis of [^{18}F]-PFH was done with a two-pot four-step procedure, but in view of the short half-life of ^{18}F (~110 min), and to make sure that the tracer is available quickly for use in the clinic, it is necessary to reduce the total time required to produce the labeled compound (4). Therefore, a new hippurate analog, *m*-cyano-*p*-[^{18}F]fluorohippurate ([^{18}F]-CNPFH), was synthesized with a single-step procedure. The biodistribution and renography properties of this labeled compound were studied in rats and compared with those of [^{18}F]PFH (4).

Related Resource Links

Related chapter in MICAD

References for [^{131}I]-iodohippurate in PubMed

References for [^{99m}Tc]-MAG$_3$ in PubMed

Clinical trials with [^{99m}Tc]-MAG$_3$

References for [^{99m}Tc]-DTPA in PubMed

Clinical trials with [^{99m}Tc]-DTPA

Synthesis

[PubMed]

The one-step nucleophilic aromatic substitution synthesis of CNPFH and its labeling with ^{18}F has been described by Pathuri et al. (4). The radiochemical yield (RCY) of the purified tracer was 73.2 ± 0.6% based on the amount of ^{18}F added to three independent synthesis reactions. The radiochemical purity (RCP) of the labeled compound was >99% as determined with reverse-phase high-performance liquid chromatography (RP-HPLC). The total time of synthesis (TOS) and specific activity (SA) of [^{18}F]-CNPFH were not reported. After purification, the tracer was dried, reconstituted in 0.9% sodium chloride, and sterilized by passing through a 0.22-μm syringe filter.

For comparison purposes, [^{18}F]-PFH was also used in some studies; however, the RCY, RCP, and SA of this tracer were not reported (4). In an earlier study, the RCY and RCP of [^{18}F]-PFH were reported to be 91%–95% and >99%, respectively, as determined with radio-HPLC (3). The TOS and the SA of ^{18}F-PFH were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No degradation products of [^{18}F]-CNPFH were generated (as determined with HPLC) when the tracer was incubated *in vitro* with human plasma for at least 1 h at 37°C (4).

HPLC analysis of urine obtained from a rat at 30 min after injection of [^{18}F]-CNPFH showed that no metabolites of the radiochemical were present in the sample (4).

These studies indicated that [^{18}F]-CNPFH was stable under *in vitro* and *in vivo* conditions.

The *in vivo* plasma protein binding and erythrocyte uptake of [^{18}F]-CNPFH were reported to be 46.1% and 16.3%, respectively (4). These values were similar to those reported earlier for [^{18}F]-PFH (3).

The partition coefficients of [^{18}F]-CNPFH and [^{18}F]-PFH in a water/*n*-octanol mixture (at pH 7.0) were determined to be −2.54 ± 0.23 and −2.53 ± 0.08, respectively (4).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]-CNPFH was studied in normal Sprague-Dawley rats as described elsewhere (4). Briefly, the animals (n = 4 rats/time point; under anesthesia) were injected with ~0.4 MBq (~15 μCi) [^{18}F]-CNPFH through the tail vein, and the rodents were euthanized at 10 min postinjection (p.i.) or 1 h p.i. to retrieve all the organs of

interest. Subsequently, the amount of radioactivity accumulated in the various tissues was determined (Table 1). Data obtained from the study were presented as percent of injected dose per gram tissue (% ID/g).

Table 1: Biodistribution of [^{18}F]-CNPFH in rats at 10 min p.i. and 1 h p.i.

Organ	Uptake of radioactivity (% ID/g)	
	10 min p.i.	**1 h p.i.**
Blood	0. 70 ± 0.13	0.03 ± 0.02
Heart	0.17 ± 0.02	0.00 ± 0.01
Lung	0.25 ± 0.05	0.01 ± 0.01
Liver	0.67 ± 0.03	0.04 ± 0.02
Spleen	0.11 ± 0.04	0.01 ± 0.02
Kidney	12.50 ± 1.10	0.44 ± 0.23
Muscle	0.06 ± 0.01	0.00 ± 0.00
Intestine	0.49 ± 0.47	0.89 ± 0.35
Urine*	37.20 ± 8.90	62.00 ± 11.30

***Data presented as % ID. ID, injected dose; p.i., postinjection. For complete data set see Pathuri et al.** (4)**.**

The tracer was rapidly cleared from blood circulation (0.70 ± 0.13% ID/g at 10 min p.i. and 0.03 ± 0.02% ID/g at 1 h p.i.), and a similar trend was noticed with all the major organs (4). The amount of radioactivity in the intestine increased from 0.49 ± 0.47% ID/g at 10 min p.i. to 0.89 ± 0.35% ID/g at 1 h p.i. The amount of label in the kidneys decreased from 12.50 ± 1.10% ID/g at 10 min p.i. to 0.44 ± 0.23% ID/g at 1 h p.i., and the level of tracer in the urine was 37.20 ± 8.90% ID and 62.00 ± 11.30% ID at 10 min p.i. and 1 h p.i., respectively. This indicated that, although a major portion of radioactivity was excreted through the renal route, some portion of the tracer was cleared through the hepatobiliary system.

Dynamic PET/computed tomography (CT) imaging with [^{18}F]-CNPFH and [^{18}F]-PFH was performed on 4 rats on two separate days (4). On the first day, the animals were injected with ~2.7 MBq (~100 μCi) [^{18}F]-CNPFH for imaging. For comparison, the same animals were injected with an equal amount of [^{18}F]-PFH for imaging on the second day. Whole-body PET scans of the animals were acquired for 30 min p.i., followed by CT imaging for 1 min. Using appropriate software, regions of interest were drawn on the images to delineate the kidneys, and a renogram analysis was performed for each rat. From the renograms it was determined that the peak activity times for [^{18}F]-CNPFH and [^{18}F]-PFH in the animals were 3.2 ± 0.4 min and 2.9 ± 0.4 min, respectively. The time to half-maximal activity was determined to be significantly higher ($P = 0.03$) for [^{18}F]-CNPFH (11.4 ± 2.8 min) than for [^{18}F]-PFH (7.1 ± 1.3 min). The PET images obtained

with [^{18}F]-CNPFH showed some accumulation of radioactivity in the liver and intestine, but no label was detected in these organs of animals injected with [^{18}F]-PFH.

From these studies, the investigators concluded that, although [^{18}F]-CNPFH was comparable to [^{18}F]-PFH to determine the renal function in rats, it produced some background signal in the PET images of the animals (4).

Other Non-Primate Mammals

[PubMed]

No reference is currently available.

Non-Human Primates

[PubMed]

No reference is currently available.

Human Studies

[PubMed]

No reference is currently available.

Supplemental Information

[Disclaimers]

No reference is currently available.

References

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