^{64}Cu-Labeled L-histidine

[^{64}Cu]-His

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Chemical name:	^{64}Cu-Labeled L-histidine	
Abbreviated name:	[^{64}Cu]-His	
Synonym:		
Agent Category:	Compound	
Target:	Copper transporter I (Ctr1)	
Target Category:	Transporter	
Method of detection:	Positron emission tomography (PET)	
Source of signal / contrast:	^{64}Cu	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

Copper (Cu) metal is not commonly available in the environment, but is an important micronutrient that is required for the activity of many mammalian intracellular enzymes (1). Presence of free Cu is toxic for the cell because it can exist in the oxidized (Cu(I)) or the reduced (Cu(II)) forms, and conversion of Cu(I) to Cu(II) under physiological conditions leads to the generation of reactive oxygen species that disrupt the normal cellular pathways. Therefore, mammals tend to maintain extremely low concentrations of the metal within tissues, which is achieved by transporting it out of the cells into the circulatory system and eventually into the bile for excretion through the hepatobiliary system (2). In the liver, the Cu transporter 1 helps in the passage of the metal into the hepatocytes, and the *ATP7B* gene product, a Cu-transporting polypeptide (for details, see

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the Related Resource Links section), is responsible for removing Cu from the liver cells for excretion into the bile. However, genetic mutations in *ATP7B* result in impaired excretion and intracellular utilization of the metal in mammals. This culminates in accumulation of toxic amounts of Cu in various organs, particularly the liver and the brain, and leads to the development of Wilson disease (WD) in humans (3).

Although treatment is available for the therapy of WD, it is challenging to diagnose the disease because there are many variations in the symptoms of this condition (2, 3). Currently WD is diagnosed only after a liver biopsy; the Cu content of the hepatic tissues can be best determined with atomic force spectroscopy, a technique that is not commonly available in the clinic (4). The unsuccessful use of ^{64}Cu for the diagnosis of WD has been attributed to the wide distribution of the element in the body and to the constant release and reuptake of the metal by different organs in the body (4). Bahde et al. hypothesized that, because the Cu excretion process is *ATP7B*-dependent, the use of ^{64}Cu complexed with histidine ([^{64}Cu]-His) was probably suitable for the diagnosis of WD because it was shown that [^{64}Cu]-His can be utilized to determine the ^{64}Cu biliary excretion capacity in animals (4). The biodistribution of [^{64}Cu]-His was investigated in Long-Evans cinnamon (LEC) rats, which have a mutated *ATP7B* and show a very high accumulation of Cu in the liver, and this biodistribution was compared with the biodistribution in Long-Evans agouti (LEA) rats that have a normally functioning *ATP7B*. In addition, dynamic positron emission tomography (PET) imaging was performed on the animals to visualize the excretion of ^{64}Cu from the liver of these animals.

Related Resource Links

Wilson disease in Kyoto Encyclopedia of Genes and Genomes (KEGG)

Clinical trials regarding Wilson disease

Copper histidine related clinical trials

Drug to treat Wilson disease

Copper transporter 1 in Online Mendelian Inheritance in Man Database (OMIM)

ATP7B gene product in OMIM

Synthesis

[PubMed]

L-Histidine was obtained from a commercial source and labeled with ^{64}Cu as described by Bahde et al. (4). The labeled product was purified on a SepPak C_{18} cartridge and eluted in water. The radiochemical purity and the radiochemical yield of the purified [^{64}Cu]-His were >95% (as determined with instant thin-layer chromatography) and 91% (based on the amount of ^{64}Cu added to the reaction mixture), respectively. The specific activity of [^{64}Cu]-His was 700–750 MBq (19.9–20.25 mCi)/4.54 μmol. The stability of the final product was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

On the basis of *ATP7B* mRNA expression in the rodents, the three genotypes of rats (n = 6 animals/genotype) used in the animal studies were as follows: the LEA (+/+) rats expressed the *ATP7B* mRNA normally, the LEC (–/–) rats were homozygous and completely lacked expression of the *ATP7B* mRNA (4), and the LEC (+/–) rats were heterozygous for expression of the mRNA because these animals had normal hepatocytes transplanted from donor LEA (+/+) rats (4). The livers and hepatocytes of the LEA (+/+) and the LEC (+/–) rats were reported to have a normal morphology, but in the LEC (–/–) rats the hepatocytes were enlarged, and the organ showed biliary proliferation and fibrosis. The Cu contents of the liver from LEA (+/+), LEC (+/–), and the LEC (–/–) rats were 20 ± 13 μg/g, 44 ± 38 μg/g, and 860 ± 58 μg/g, respectively, indicating that the LEC (–/–) animals accumulated high levels of Cu in the organ.

To investigate the biodistribution of radioactivity from [^{64}Cu]-His in the different genotypes of rats (n = 9 animals/genotype), the rodents were injected with 3.7–5.5 MBq (100–150 μCi) of the tracer through the intrasplenic route (4). Bile and the organs of interest were collected from the rodents at various time points, ranging from 0 min to 24 h post-injection (p.i.), to determine the amount of accumulated radioactivity in the bile and the different tissues. All results were presented as percent of total injected dose per gram tissue (% ID/g). The rate of radioactivity clearance from the blood was rapid, medium, and very slow in the LEC (–/–), LEC (+/–), and LEA (+/+) rats, respectively (Table 1). In general, the accumulation of radioactivity was highest in the liver, followed by the kidney and the spleen for all the rat genotypes. As expected, the liver of LEC (–/–) rats had a significantly higher ($P < 0.05$) amount of label compared with the organs from either the LEA (+/+) or the LEC (+/–) animals. The excretion of label into the bile of the different animals was studied for up to 24 h p.i. as described by Bahde et al. (4). Both the LEA (+/+) and the LEC (+/–) animals showed a gradual and comparable secretion of radioactivity into the bile during this period; however, the LEC (–/–) animals showed no secretion of label into the bile for the entire duration of the study and showed a significantly increased accumulation ($P < 0.05$) of the tracer up to 24 h p.i. This indicated that the biliary excretion of radioactivity in the LEA (+/+) and the LEC (+/–) rats was due to the presence of an active *ATP7B* gene.

Table 1: Amount of radioactivity (% ID/g) in blood (4)**.**

Genotype	Blood		Rate of clearance
	Time p.i.		
	45 min	24 h	
LEA (+/+)	74 ± 5	71 ± 9	Very low
LEC (+/–)	75 ± 5	50 ± 12*	Medium
LEC (–/–)	61 ± 5	9 ± 2*	Rapid

***P* < 0.05 compared to the amount of label at 45 min p.i.**

For PET imaging, anesthetized rats were injected with 18.5 MBq (500 μCi) [^{64}Cu]-His as before, and dynamic images of the animals (n = 3 rats/genotype per time point) were acquired at 1 h, 3 h, and 24 h p.i. as described elsewhere (4). From the images it was clear that the level of radioactivity accumulated in livers of the LEA (+/+) and LEC (+/–) rats at 1 h p.i. had decreased by 3 h p.i. and was further reduced by 24 h p.i. The loss of radioactivity from the liver was consistent with the appearance of the tracer in the bile of these animals during the same period. In the LEC (–/–), rats the amount of label in the liver gradually increased from 1 h p.i. to 24 h p.i., indicating that there was little to no loss of ^{64}Cu from this organ in these animals for up to 24 h p.i.

In a separate study, it was shown that acute liver injuries in normal LAE (+/+) rats (n = 6 animals) or chronic liver injuries in normal F344 rats (n = 9 animals) did not alter the uptake and excretion of ^{64}Cu in the liver of these rodents (4). Similar observations were made when LAE (+/+) rats were treated with drugs that increased the flow of bile (sodium valproate or hydrocortisone) in these animals (4). In another study, it was observed that the clearance of ^{64}Cu from the blood of rats (number of animals not mentioned) with cirrhotic livers (induced with repeated carbon tetrachloride treatment) was slower than that in healthy rats, and the amount of label present in the diseased liver was lower compared to that in the hepatic tissue of the LEC (–/–) animals (4).

From these studies, the investigators concluded that [^{64}Cu]-His can be used with PET imaging to detect WD in rodents (4).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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References

1. Tsigelny I.F., Sharikov Y., Greenberg J.P., Miller M.A., Kouznetsova V.L., Larson C.A., Howell S.B. *An all-atom model of the structure of human copper transporter 1.* Cell Biochem Biophys. 2012;63(3):223–34. PubMed PMID: 22569840.
2. Weiss K.H., Stremmel W. *Evolving perspectives in Wilson disease: diagnosis, treatment and monitoring.* Curr Gastroenterol Rep. 2012;14(1):1–7. PubMed PMID: 22083169.
3. Bennett J., Hahn S.H. *Clinical molecular diagnosis of Wilson disease.* Semin Liver Dis. 2011;31(3):233–8. PubMed PMID: 21901653.
4. Bahde R., Kapoor S., Bhargava K.K., Schilsky M.L., Palestro C.J., Gupta S. *PET with 64Cu-Histidine for Noninvasive Diagnosis of Biliary Copper Excretion in Long-Evans Cinnamon Rat Model of Wilson Disease.* J Nucl Med. 2012;53(6):961–8. PubMed PMID: 22577234.