Hyperpolarized [^{13}C]-2-hydroxyethylpropionate

HP[^{13}C]HEPP

Huiming Zhang, PhD[1]

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Chemical name:	Hyperpolarized [^{13}C]-2-hydroxyethylpropionate	
Abbreviated name:	HP[^{13}C]HEPP	
Synonym:	^{13}C-CM, AH-110626	
Agent category:	Small molecule	
Target:	Other	
Target category:	Other -metabolism	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal/contrast:	^{13}C	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals	No structure is available in PubChem.

Background

[PubMed]

The signal of nuclear magnetic resonance (NMR) is proportional to the thermal equilibrium polarization of nuclear spins. As a function of magnetic field strength and temperature, the thermal equilibrium polarization is normally very low. For instance, the polarization level (the population difference) is 5×10^{-6} for ^{1}H and 1×10^{-6} for ^{13}C at 1.5 T and at body temperature. Because the thermal equilibrium polarization increases proportionally with the magnetic field strength, magnetic resonance imaging (MRI) systems at field strengths of 3–11.7 T have been developed. A totally different approach for increasing the polarization of spins is to create an artificial, non-equilibrium

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

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distribution of nuclear spins called the hyperpolarized state (1). In this state, the polarization of spins can be increased by a factor of ~10^5 compared with that in the thermal equilibrium state. This approach has been used to hyperpolarize a wide range of organic substances containing ^{13}C by either parahydrogen-induced polarization (PHIP) (2) or by dynamic nuclear polarization (DNP) (3). The produced ^{13}C signal allows for practical medical and diagnostic imaging (4). The potential applications of hyperpolarized ^{13}C imaging include vascular imaging, perfusion imaging, catheter tracking and visualization, interventional applications, and metabolic/molecular imaging (1).

The PHIP method increases the nuclear polarization by a chemical reaction of parahydrogen with a substrate containing double or triple bonds (5). In parahydrogen, the two hydrogen nuclei are oriented antiparallel. This is a non-equilibrium state in which the magnetic moments of the hydrogen nuclei cancel mutually (1). The parahydrogen molecule is added as a whole unit onto substrates by rhodium-catalyzed hydrogenation. Then the non-equilibrium spin polarization of parahydrogen is converted to the nuclear polarization of a vicinal ^{13}C nucleus by diabatic-adiabatic magnetic field cycling (6, 7) or by radiofrequency (RF) pulses (8, 9). The magnetic field-cycling method involves two consecutive steps. The magnetic field is first suddenly dropped to nearly zero (<10 nT) from a high field value, followed by an adiabatic increase of the magnetic field up to 100 μT (7). By recycling the external magnetic field strength, the proton-carbon spins are brought into the strong coupling regime where the polarization is transferred from parahydrogen to carbon nuclei. The RF pulse sequence method uses the insensitive nuclei enhanced by polarization transfer (INEPT) mechanism to accomplish the polarization transfer between parahydrogen and ^{13}C nuclei (8, 9). Currently, polarization levels of 20–30% can be obtained by the PHIP method for a substrate such as 2-hydroxyethylacrylate (1). Its hydrogenated product (2-hydroxyethylpropionate, abbreviated as HP[^{13}C]HEPP) can be injected into subjects at a concentration range of 0.3 to 1.2 M in 2–3 ml. The injected HP[^{13}C]HEPP can reach hearts and lungs in <10 s in rodents. An estimated concentration is in the range of 2 to 40 mM for the first pass. This provides a reasonable time window to collect signals in major organs and access changes in molecular structures of metabolic process.

A major difference between hyperpolarized ^{13}C MRI and conventional MRI is that the magnetization of hyperpolarized ^{13}C is created outside the MRI imager in a polarized system (10). Once the hyperpolarization has been created, the polarization will strive to return to the thermal equilibrium level at a rate governed by T_1 relaxation time, which typically ranges from a few seconds to several minutes for ^{13}C depending on the functional groups present. The corresponding time window for imaging is approximately a few minutes. Because 1.1% natural abundance of ^{13}C produces negligible ^{13}C signal, there is as a result virtually no background signal other than noise from the patient and the coil/receiver system. The injected HP[^{13}C]HEPP generates a ^{13}C signal that is linearly proportional to its concentration (10). In this respect, hyperpolarized ^{13}C MRI behaves in a manner similar to modalities such as positron emission tomography (PET) and single-photon emission tomography (SPECT), where the signal amplitude is directly proportional to concentration of the agents. However, PET and SPECT have much higher

sensitivities, allowing for detection of tracers at 10^{-8} M. The lack of background signal is advantageous in many applications such as angiography and perfusion, in which collection of additional proton images is required to provide anatomic interpretations. The small molecular size of HP[^{13}C]HEPP qualifies it as an extracellular fluid (ECF) MRI contrast agent (10), suitable for pharmacokinetic tracing. HP[^{13}C]HEPP remains mainly within the vascular bed during the first few circulations in the body. Subsequently, HP[^{13}C]HEPP is distributed into the extracellular space and is finally excreted through the kidneys.

Synthesis

[PubMed]

Goldman et al. detailed the procedure of generating HP[^{13}C]HEPP (7). First, parahydrogen at ~97% purity was produced by passing hydrogen gas through a commercial catalyst (Ironex O-P catalyst or C*Chem) at a temperature of 14 K. A reactor chamber was pressurized with the parahydrogen to 10 bar and warmed to 60°C to speed the hydrogenation process. Next, ^{13}C-labeled 2-hydroxyethylacrylate (molecular weight ~120 Da) and a rhodium catalyst were injected into the reaction chamber for hydrogenation to yield 2-hydroxyethylpropionate. For the field-cycling technique (7), the producing liquid was transferred into a low-field chamber of 10 μT and held for 0.5 s; then the field was decreased to 30 nT in 1 ms and subsequently increased exponentially back to 100 μT in 1 s. This polarized solution was filtered to remove the catalyst; a fraction of the solution was used for polarization calibration by NMR and the rest was transferred to a syringe for imaging purposes. The whole process was controlled by computer. For the RF pulse irradiation technique (9), the produced liquid was filtered and then subjected to an INEPT-type RF pulse sequence, which transferred the spin order from the parahydrogen on the hydrogenated molecules to the vicinal quaternary ^{13}C nuclei. Both techniques provided a maximum ^{13}C polarization at 20–30%, which was ~2×10^5 times the thermal equilibrium value (7).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The ^{13}C relaxation times T_1 and T_2 of HP[^{13}C]HEPP were 45–60 s and 5–6 s *in vivo* at body temperature, respectively (10).

Animal Studies

Rodents

[PubMed]

The use of HP[^{13}C]HEPP as tracer was demonstrated with magnetic resonance angiography in the neck and head in guinea pigs (7). A 3-ml aqueous solution containing

0.5 M HP[^{13}C]HEPP was injected into the aortic arch through an arterial catheter in 2 s. The polarization of ^{13}C was obtained with the magnetic field cycling method, and its value was ~24%. The ^{13}C images of the head were produced by use of the true-fast imaging with steady-state precession (trueFISP) method on a 1.5-T imager, which exhibited a well-defined network of blood vessels when HP[^{13}C]HEPP passed through the vasculatures.

Other Non-Primate Mammals

[PubMed]

HP[^{13}C]HEPP was used in the coronary angiography in five pigs (average weight = 31 ± 4 kg) during a cardiac interventional MRI procedure (10). A 5-ml aqueous solution containing 0.5 M HP[^{13}C]HEPP was injected through a coronary artery. The polarization of ^{13}C (~25–30%) was obtained by the magnetic field cycling method. The ^{13}C images were collected on a 1.5-T imager with the use of a fully balanced steady-state free precession (bSSFP) pulse sequence. The coronary arteries were well depicted with signal/noise ratios of 10–40. HP[^{13}C]HEPP was also used to perform real-time catheter tracking in pigs at 1.5 T (11). A 20% polarization of ^{13}C was obtained by RF pulse irradiations to facilitate the polarization transfer from the proton nuclei to ^{13}C nuclei. Under X-ray fluoroscopic guidance, a catheter over a guidewire was inserted into the left renal artery or the aortic arch. Coronal and sagittal ^{13}C projection images of the catheter were acquired in an interleaved fashion while moving the catheter through the aortic arch of the pig. The entire length of the moving ^{13}C catheter could be visualized *in vivo* using a standard bSSFP interleaved dual projection imaging protocol. The movement of catheter was visualized with a frame rate of one dual projection frame per 600–800 ms with typical signal/noise reduction ratios of 70–90.

The HP[^{13}C]HEPP was used to image pulmonary vasculatures and parenchyma in pigs (9). High spatial and temporal resolution images of pulmonary perfusion were obtained at 1.5 T with this contrast technique. A partially deuterated HP[^{13}C]HEPP (D-HP[^{13}C]HEPP), which has a T_1 relaxation time of 138 ± 8 s, longer than the 45 s in the non-deuterated analog, was used in the study. After injection of 5 ml of 0.3-M D-HP[^{13}C]HEPP into the femoral vein in 5 s, the images displayed the time-dependent behavior of the injected D-HP[^{13}C]HEPP, which flowed through the inferior vena cava and into the pulmonary arteries before being distributed throughout the lung parenchyma. HP[^{13}C]HEPP was used to measure renal cortical blood flow in rabbits at 1.5 T (12). A 0.30-M HP[^{13}C]HEPP solution with polarization of 25–30% was injected in 1 s *via* ear veins. The renal cortical blood flow was estimated to be 5.6 ± 1.4 ml/min per ml of kidney tissues, and the mean transit time in the renal arteries was determined to be 1.45 ± 0.07 s.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

HL 077241, RR002305

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