Molecular Imaging

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HIGHLIGHTS

- Aqueous hyperpolarized ^{13}C contrast media prepared by Parahydrogen Induced Polarization (PHIP) for *in vivo* use
- Non-toxic hyperpolarized gas produced by heterogeneous (het) PHIP
- Xenon Induced Polarization (XIP) of ^{13}C biomolecules using hyperpolarized ^{129}Xe produced by clinical ^{129}Xe polarizer using Spin Exchange Optical Pumping (SEOP)

HOW TO HYPERPOLARIZE AGENTS

TARGET AUDIENCE: Biochemists, Pulmonologists, Chemists, Physicists

OBJECTIVE: Broaden the knowledge about hyperpolarized contrast agent production by other hyperpolarization methods: PHIP, SEOP, XIP

PURPOSE: Hyperpolarization temporarily increases nuclear spin polarization P significantly (i.e. orders of magnitude) above equilibrium polarization level endowed by the main detection field B_0. This enormous polarization increase translates in the corresponding increase of Magnetic Resonance (MR) sensitivity of exogenous compounds. Biomolecules (e.g. pyruvate, choline, succinate, etc.) (1,2) and inert gases (^3He, ^{129}Xe, etc.) (3,4) with long spin-lattice relaxation times T_1 can be used to preserve hyperpolarized state with useful imaging lifetime ranging from tens of seconds (5) to hours (6). These hyperpolarized compounds can be used as contrast media for molecular imaging of metabolism and organ function. Fundamentally, hyperpolarized contrast agents can provide better understanding of molecular pathways than Positron Emission Tomography (PET) contrast agents, because MR can non-invasively discern not only the uptake of hyperpolarized molecule, but also its metabolic product(s) (i.e. chemical environment of the hyperpolarized spin label) (2,5,7) and tissue compartmentalization (i.e. physical environment) (8). Furthermore, because nuclear spin polarization of hyperpolarized spin state is not endowed by the detection magnetic field B_0, low-field MRI (< 0.1 T) of hyperpolarized contrast media can provide greater sensitivity than that of conventional high-field detection (9,10) mitigating the need for B_1 and B_0 mapping, and potentially enabling true sub-minute MR examination without requirement for expensive MRI scanner and specific absorption rate (SAR) concerns (11).

While dissolution Dynamic Nuclear Polarization (DNP) is the most advanced hyperpolarization technique, other methods can also be used to hyperpolarize contrast agents for molecular imaging of metabolism and function. The goal of this presentation is to cover the fundamentals of two other hyperpolarization techniques: (i) Parahydrogen Induced Polarization (PHIP) (12,13), and (ii) Spin Exchange Optical Pumping (SEOP) from the perspective of preparation of a batch of aqueous/injectable of gaseous/inhalable hyperpolarized contrast agent for molecular imaging in preclinical or clinical setting.

METHODS AND RESULTS: Conventional PHIP uses a ^{13}C enriched molecular precursor with a double or triple carbon-carbon bond for molecular addition of parahydrogen gas (Fig. 1A) using Rh(I) catalyst. Parahydrogen provides the source of hyperpolarization. The molecular addition is required to be fast on the time scale of a few seconds (14) in order to preserve hyperpolarization of nascent protons of hyperpolarized product. The final step of PHIP process is polarization transfer from nascent protons to ^{13}C nucleus, which is typically a long-lived carboxyl site with T_1 up to 100 s (15,16). PHIP produces ^{13}C contrast agents with ^{13}C %P up to

50% (17). The entire process can be conducted in aqueous medium allowing preparation of a batch of contrast agent suitable for *in vivo* use (18). Further heterogeneous manipulations enable isolation of pure ^{13}C hyperpolarized agents free from Rh(I) catalyst (19). The first generation of PHIP contrast agents for biomedical use have been limited to a few compounds, because of the chemical prerequisite of unsaturated carbon-carbon bond adjacent to long-lived ^{13}C site (Fig. 1) prohibiting the use of –OH groups adjacent of C=C motif (Fig. 1A). Hydroxyl group is found in many biological compounds: lactate, choline, etc. As a result, only a few contrast agents have been developed: 2-hydroxyethyl 1-^{13}C-propionate (HEP) (20), tetrafluoro-1-^{13}C-propionate (TFPP) (21), ^{15}N-propargylcholine (22), 1-^{13}C-succinate (SUX) (23,24) and others (25). Some were successfully validated *in vivo* for imaging of vasculature (26), cancer (27), and plaque deposits (8). However, the recent demonstrations of protected –OH group use in PHIP precursor (28,29) adjacent to the unsaturated carbon-carbon bond significantly expanded the reach of biomolecules amenable by conventional PHIP: protected ethanol (29), lactate (14), choline (30), and potentially many others.

While many molecules can be hyperpolarized using conventional PHIP, there are other key requirements in addition to biochemistry discussed above. First, the agents must have sufficiently long T_1 to penetrate biochemical pathway *in vivo*. Deuteration of the molecular precursor allows significantly extending the lifetime of hyperpolarized state from several seconds (23) to tens of seconds (24). Second, high level of hyperpolarization (> 5%) should be generated for sufficient increase of MR signal *in vivo*. This is achieved via a second added benefit of deuteration of the molecular precursor, which simplifies spin-system to three spins: two nascent protons and ^{13}C and the use of highly specialized RF pulse sequences (20,31) for polarization transfer (Fig. 1A) and PHIP polarizers. A typical PHIP polarizer (9,16,32,33) (i) maintains a low field of a few mT over a high-pressure chemical reactor (ii) with hydrogenation chemistry controlled by an automated gas/liquid valve manifold and (iii) with RF pulses enabled by large volume RF coils for efficient polarization transfer.

Other broad group of PHIP approaches utilizes heterogeneous (*het*) catalysts including those based on Rh(I) allowing ultra-fast hydrogenation of gases (34,35). The use of *het* catalysts pioneered by Kovtunov and Koptyug (36) enables PHIP production of pure non-toxic hydrocarbons for gas imaging *in vitro* and potential *in vivo* use similarly to SEOP of inert gases, e.g. ^{3}He, ^{129}Xe, etc.

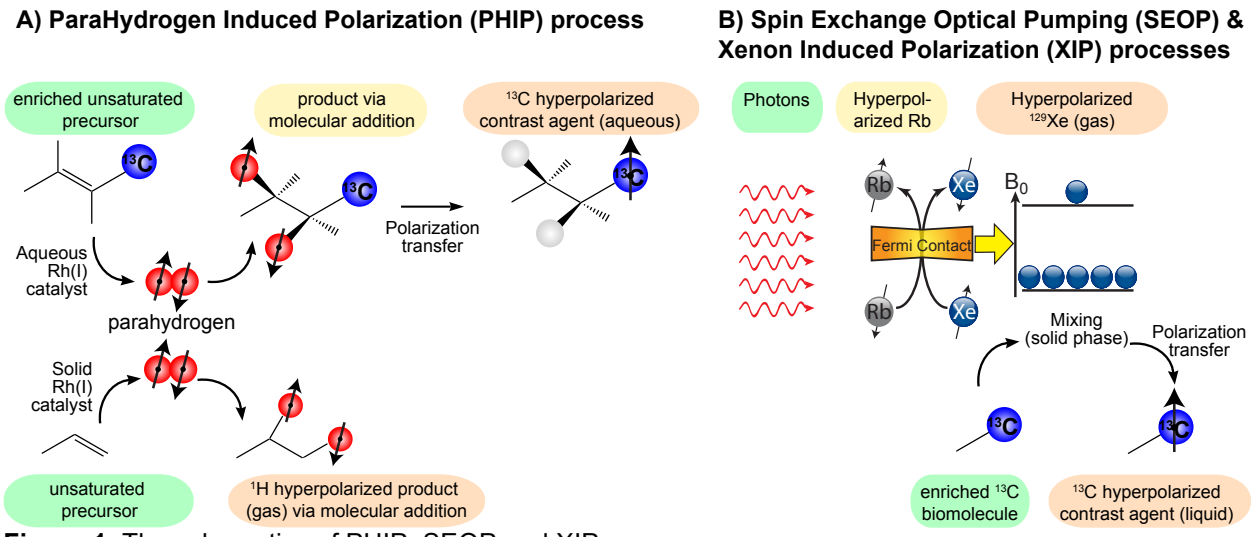

Figure 1. The schematics of PHIP, SEOP and XIP processes.

SEOP has been available for decades (3). While ^{3}He supply became very limited, a number of SEOP ^{129}Xe polarizers have been demonstrated recently (37,38) including a recent development of open-source batch ^{129}Xe polarizer (6) mitigating the need for ^{129}Xe cryo-freezing (6,39). Production of ^{129}Xe by SEOP aims to fulfill several requirements for biomedical use: (i) negligible gas contamination by Rb for safe patient administration, and (ii) maximizing %*P* of hyperpolarized ^{129}Xe in one 0.5-1.0 L batch of produced gaseous contrast agent at maximum ^{129}Xe partial pressure to maximize the payload of ^{129}Xe magnetization for pre-clinical and clinical use. While hyperpolarized ^{129}Xe as a contrast agent enables a variety of clinical MRI exams reporting on lung function, e.g. ventilation, perfusion, etc. (4,40), it can also be used as a source of hyperpolarization (Fig. 1B). ^{13}C hyperpolarized CS_2 was demonstrated by dissolving CS_2 in hyperpolarized liquid Xe (41). Furthermore, biomolecules (e.g. ^{13}C-acetic acid) can be mixed with hyperpolarized xenon in the gas phase followed by mixture condensation into the solid phase and polarization transfer from ^{129}Xe to ^{13}C (42) enabling Xenon Induced Polarization (XIP). As a result, SEOP derived ^{129}Xe hyperpolarization of clinical grade Xe can be transferred to ^{13}C enriched biomolecules resulting in pure hyperpolarized liquids (42) that can be potentially used as metabolic contrast agents for molecular imaging.

DISCUSSION AND CONCLUSION: PHIP is inherently a relatively low-cost hyperpolarization technology, which has been successfully validated via pre-clinical molecular imaging. While it had a significant limitation of amenable to hyperpolarization biomolecules, this limitation has been alleviated by the recent use of –OH protected unsaturated PHIP precursors, the use of advanced heterogeneous procedures for production of pure hyperpolarized biomolecular contrast agents, and the use of *het*-PHIP for production of non-toxic hyperpolarized gases.

Hyperpolarized ^{129}Xe is a useful clinical contrast agent for functional lung imaging. Furthermore, clinical grade hyperpolarized ^{129}Xe can serve as a source of hyperpolarization for production of pure hyperpolarized biomolecules via XIP.

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