Producing radical-free hyperpolarized solutions for in vivo magnetic resonance

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Introduction

Dissolution dynamic nuclear polarization[1] (DNP) has become an attractive technique for achieving tremendous gain in signal-to-noise ratio in MRI and MRS[2]. Stable radicals are required as polarizing agents for the DNP process but they are undesirable once the biomolecules of interest are hyperpolarized. These stable radicals need to be removed from the hyperpolarized solutions for at least two major reasons: first, they reduce the nuclear polarization of the DNP-enhanced biomolecules through paramagnetic relaxation processes and second, the toxicity of the radicals raises potential health issues for *in vivo* applications. Recently, thermoresponsive spin-labeled hydrogel (SL-hydrogel) was used to polarize nuclear spins via liquid-state DNP (Overhauser effect)[3]. A thermoresponsive hydrogel is a special polymer network soluble in water and alcohols which can be labeled with stable radicals. Upon heating, the hydrogel quickly shrinks and the solvent is expelled from the polymer network. Since the polarizing agents are covalently bound to the hydrogel, the extracted hyperpolarized solutions do not contain stable radicals. In the present project we show that thermoresponsive SL-hydrogel can also be used to produce radical-free hyperpolarized solutions via dissolution DNP.

Methods

A homogenous mixture of 500 µl 9:1 d_{10}-tert-butanol / D_2O (v/v) containing 15% SL-hydrogel (equivalent to a radical concentration of 6.8 mM) was rapidly frozen in liquid nitrogen and placed in a 5 T custom-designed DNP polarizer[4]. The DNP process was carried out at 1±0.05 K by irradiating the sample at 140.18 GHz (35 mW). The solid-state polarization build-up was monitored by applying a 5° pulse every 5 min. After 5 h of polarization, the tert-butanol was rapidly dissolved in superheated D_2O and transferred within 2 s into a home-built separator/infusion pump located inside a 9.4T scanner (INOVA, Varian) (Fig.1). The characteristic decay time of the 1-^{13}C signal of tert-butanol was measured using a custom-built probe installed on the separator/infusion pump (5° pulse every 3 s). For comparison, 9:1 d_{10}-tert-butanol / D_2O (v/v) frozen beads containing 33 mM TEMPO radicals were polarized, dissolved and measured at the same conditions.

Results and discussion

The characteristic ^{13}C solid-state build-up time constant was measured to be 5600 ± 750 s in samples polarized with SL-hydrogel matrices. The solid-state enhancement was 20±1 for all samples, corresponding to a room-temperature liquid-state enhancement of 6000±300. The ^{13}C longitudinal relaxation time T_1 was deduced from the decay of the signal as a function of time (fig.2) and was compared to the decay measured in hyperpolarized solutions obtained from dissolved TEMPO-doped beads (fig.2). The ^{13}C relaxation constant was much longer (112±2 s) for tert-butanol polarized with the SL-hydrogel than for tert-butanol polarized with TEMPO radicals (29±0.1s). The 1-^{13}C T_1 of d_{10}-tert-butanol was also measured in thermally polarized (degassed and non-degassed) 9:1 d_{10}-tert- butanol / D_2O (v/v) samples on a high-resolution 9.4T (Bruker) system using a saturation recovery pulse sequence (fig.3). The results confirm that not only the solution localized in the infusion/separator pump and ready to be infused is free of stable radical, but it also demonstrates that the solution is free of paramagnetic species and in particular oxygen ions.

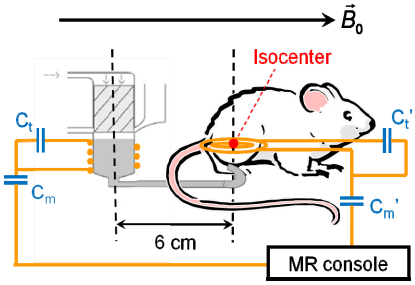

Fig 1: Sketch of the experimental setup inside the magnet bore. 6 cm separate the center of the ^{13}C coil wound around the pump from the animal ^{13}C surface coil.

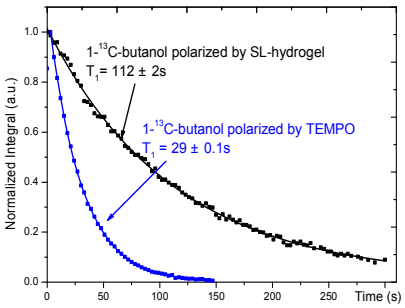

Fig 2: 1-^{13}C signal decays of d_{10}-tert-butanol hyperpolarized using SL-hydrogel (black) and TEMPO (blue).

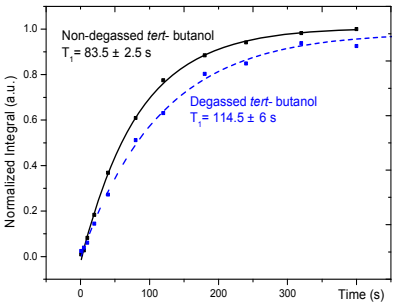

Fig 3: ^{13}C T_1 measured using a saturation recovery scheme in thermally polarized 9:1 d_{10}-tert butanol / D_2O (v/v) solutions.

Conclusion

We demonstrated that spin-labeled thermoresponsive hydrogel allows for producing radical-free hyperpolarized solutions via dissolution DNP. This method has a high potential for future clinical applications of DNP since it not only leads to reduce polarization losses but it also directly solve the question of toxicity linked to the presence of radicals in the hyperpolarized solutions. We applied this method to hyperpolarize ^{13}C-labeled tert-butanol which has been recently shown to be a promising contrast agent for *in vivo* perfusion imaging[5].

Acknowledgements

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