Localized in vivo hyperpolarization transfer experiments

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Introduction

Dissolution dynamic nuclear polarization[1] (DNP) has become an attractive technique for studying biological transformations *in vivo*[2]. However, the time delay between the DNP process and the *in vivo* measurements associated to dissolution DNP experiments restricts the application of this technique to precursors possessing molecular sites with long T_1 values. As a consequence, *in vivo* DNP-enhanced studies were limited so far to non-protonated low-γ-nuclei such as carbonyl ^{13}C's or ^{15}N-labeled quaternary amines. It has been recently shown in *in vitro* studies that nuclear hyperpolarization can be transferred to its neighboring nuclei prior to detection[3], thus significantly enhancing the polarization of nuclei that do not retain their hyperpolarized state following sample shuttling. Here we present a new localized *in vivo* protocol to perform homo- or hetero- nuclear polarization transfer from the long T_1 hyperpolarized nuclear spins to their neighboring molecular sites for detection.

Methods

Carbon nuclear spins in frozen glassy solutions of 1-^{13}C and of $^{13}C_2$ labeled acetate were dynamically polarized using a custom-designed DNP polarizer operating at 5T and 1 ± 0.05K. Once ^{13}C spins reached maximal polarization, the frozen mixtures were rapidly dissolved and transferred into an infusion pump capable of injecting 2.2 mL of hyperpolarized solution *in vivo* within 9 s[4, 5]. Sprague-Dawley rats (350 g) were anesthetized using 1.5% isoflurane and their physiology was monitored during the experiments. The femoral vein was catheterized for injection of the hyperpolarized substrate into the animals. Measurements were carried out on a 9.4 T/ 31 cm actively shielded animal scanner (Varian/Magnex) using home-built quadrature ^{1}H surface coils and a 10mm diameter ^{13}C surface coil. In all experiments data acquisition started immediately after infusion, i.e., 12 s after dissolution.

Results

Homonuclear (^{13}C to ^{13}C) and heteronuclear (^{13}C to ^{1}H) fully adiabatic polarization transfer experiments were designed based on the INEPT like pulse sequence[6] and tested *in vivo* in the rat brain. Localization was achieved using an outer volume suppression block[7], followed by J-coupling mediated transfer from the hyperpolarized carbonyl ^{13}C to its J-coupled neighboring spins for detection. Adiabatic RF pulses were used to compensate for the B_1 inhomogeneity of the surface coil. Homonuclear polarization transfer was mediated via $^1J_{CC}$ and was applied *in vivo* following the infusion of hyperpolarized $^{13}C_2$ acetate (Fig.1, n=4). The heteronuclear transfer was carried out through $^2J_{CH}$ coupling and tested *in vivo* after infusing hyperpolarized 1-^{13}C acetate (Fig.2, n=4). Water suppression for proton detection in the heteronuclear experiments was achieved by incorporating coherence selective gradients[8] into the pulse sequence.

Discussion and conclusion

The indirect detection scheme demonstrated in the present study provides additional spectroscopic information from different chemical sites and has the potential to assert the assignment of metabolites resonance peaks detected in hyperpolarized MR experiments. In addition, this type of detection can lead to improved spectral resolution by probing different nuclear spins of hyperpolarized precursors and their metabolites, e.g. methyl ^{13}C or ^{1}H in ^{13}C-acetate or ^{1}H in ^{15}N-choline[9] and their respective metabolites[9].

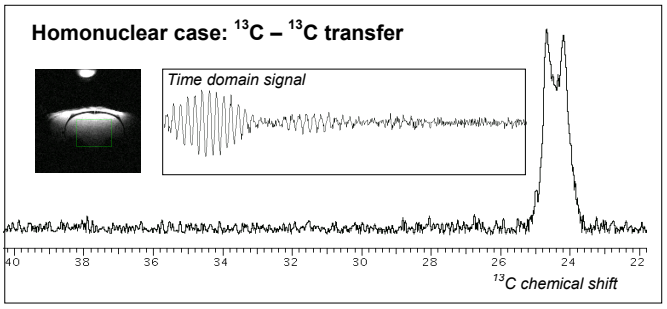

Fig 1: *In vivo* single scan acquisition after polarization transfer from the carboxyl ^{13}C to the methyl ^{13}C following the infusion of hyperpolarized $^{13}C_2$-acetate. The signal was localized in the area denoted in green on the ^{1}H image. The shape of the time domain data confirms that the signal arises from the transfer. The ^{13}C-^{13}C coupling pattern was observed while the $^1J_{CH}$ interaction was decoupled.

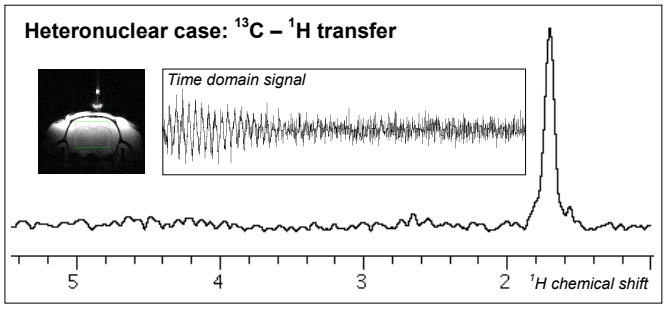

Fig 2: *In vivo* single scan acquisition after polarization transfer from the carboxyl ^{13}C to the ^{1}H following the infusion of hyperpolarized 1-^{13}C acetate. The signal was localized in the area denoted in green on the ^{1}H image. The shape of the time domain data confirms that the signal arises from the transfer.

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