Detection and imaging of hyperpolarized 6-lithium in the rat brain *in vivo*

R. B. van Heeswijk[1], K. Uffmann[1], A. Comment[2], F. Kurdzesau[2,3], C. Perazzolo[1], C. Cudalbu[1], S. Jannin[2], T. Konter[3], P. Hautle[3], B. van den Brandt[3], J. J. van der Klink[2], G. Navon[4], and R. Gruetter[1,5]

[1]Laboratory for Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [2]Laboratory for Physics of Nanostructured Materials, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [3]Paul Scherrer Institute, Villigen, Switzerland, [4]School of Chemistry, Tel Aviv University, Tel Aviv, Israel, [5]Departments of Radiology, Universities of Lausanne and Geneva, Switzerland

Introduction

Lithium salts are used for the treatment of manic/depressive (bipolar) and depressive disorders. Of the two natural occurring Li isotopes, ^{6}Li is known to have a long T_1 (1) despite being a spin-1 system, owing to its low quadrupolar moment. We recently showed that using dynamic nuclear polarization (DNP, 2), hyperpolarized lithium-6 chloride retains a very long longitudinal relaxation time on the order of two minutes after dissolution, and an extremely high sensitivity to detect contrast agents at nanomolar concentrations (3). The aim of the present study was to determine the relaxation and enhancement of hyperpolarized lithium in vivo, and secondly to determine the spatial extent of lithium-6 in rat brain.

Materials and Methods

Male Sprague-Dawley rats (w = 325 ± 70 g) were anesthetized using 1.5% isoflurane and a femoral vein was catheterized for injection. Blood pressure, respiration rate and temperature were maintained within normal range. A quadrature ^{1}H coil with a single 4-loop ^{6}Li coil was used. The animal was then inserted into a Varian Inova 9.4T 31 cm bore actively-shielded animal spectrometer.

Lithium-6 chloride was dissolved in a D_2O-ethanol mixture at a concentration of 15 M together with 33 mM of TEMPO. 50 µl of this mixture was then polarized at 3.35 T and 1.2 K using the polarizer described in ref. 4. After dissolution into 5 ml of D_2O the concentration of lithium was ~100 mM. Within 6 s this dissolved sample was automatically transferred to a phase separator placed in the bore of the 9.4 T scanner. A remote controlled pump then injected 2.5 ml of the sample into the rat femoral vein over 8 s. The complete sample was thus injected into the rat within 14 s of the start of the dissolution process.

To estimate the *in vivo* T_1 of ^{6}Li, spectra were acquired on 4 rats using a 3 ms 10° BIR4 pulse with 3 s interpulse delay.

The FIDs were postprocessed with a modest 0.045 s Gaussian curve and corrected for the loss of magnetization due to the 10° RF pulses.

Spectroscopic imaging was performed on 4 rats using an Echo-planar SI sequence based on FASTESTMAP (5). Briefly, following 10° BIR4 pulses for excitation two hyperbolic secant pulses selecting a 10 mm slice with a repetition time of 500 ms (8 s total acquisition), FOV was 30x30 mm with 16x16 in-plane resolution. Postprocessing consisted of 2x zerofilling in all directions. The image was smoothened by interpolating the data 4 times.

Results and Discussion

The polarization in the cryostat reached 5% (corresponding to roughly 11000 times amplification compared to room temperature polarization at 9.4 T). ^{6}Li was still discernible above the noise level after 3 min (Fig. 1a) and had a maximum SNR of 60. A curve of the signal integrals corrected for RF pulse effects (Fig. 1b) indicates the feasibility to detect ^{6}Li signal even after 5 min. The fitted apparent relaxation time was T = 32 ± 3 for the first minute, while it was T = 94 ± 16 s afterwards. The different decay rates were attributed to recirculation effects. The spectroscopic imaging sequence shows signal (Fig. 2) in the vein above the brain (dark red) but also signal distribution in the brain consistent with the depth sensitivity profile of the surface coil used.

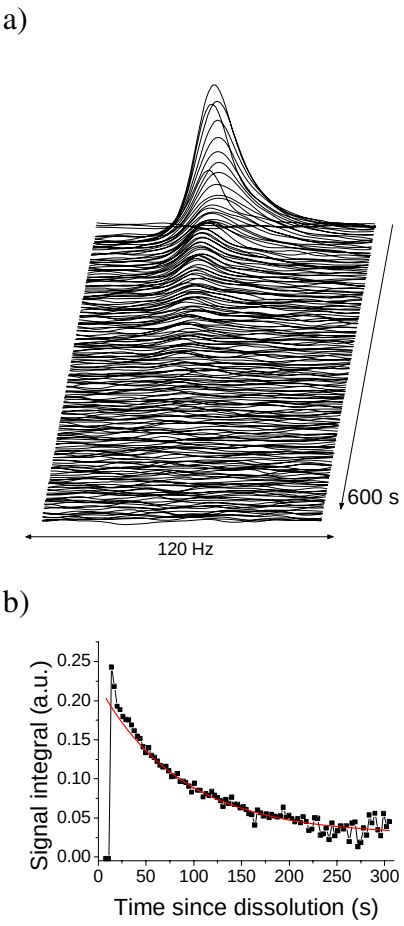

Figure 1. a) *Stack plot of the ^{6}Li signal over time. After an initial small phase and frequency change, it appears stable.* ***b)*** *Decay curve of the signal integrals corrected for the previous RF pulses. A fit for the latter part (60-300 s) is shown, which can be seen to mismatch with the initial points.*

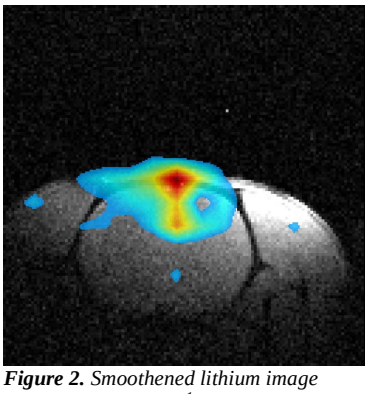

Figure 2. *Smoothened lithium image projected on top of a ^{1}H transversal image. Note the limited spatial sensitivity of the Li-coil and the signal still originating in the brain.*

Conclusions

Lithium-6 can be detected *in vivo* using DNP hyperpolarization and appears to distribute in the brain. The long T_1 of ^{6}Li opens the perspective of imaging contrast agents at very low concentrations (3). In addition, very slow perfusion (which is not measurable using hyperpolarized ^{13}C), such as that encountered in tumors can be assessed using ^{6}Li.

Acknowledgements

Supported by Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL and the Leenaards and Jeantet Foundations; NIH grant R01NS42005 and SNSF grant 3100A0-116220.

References

1. Wehrli, J Magn Reson 23 (1976) p527
2. Abragam and Goldman, Rep Prog Phys 41 (1978) p395
3. Van Heeswijk e.a., Magn Reson Imag 25:6 (2007) p821
4. Comment e.a., Conc Magn Reson 31B (2007) p255
5. Gruetter, Magn Reson Med 29 (1993) p804