

In vivo localized ^{15}N MRS detection of hyperpolarized ^{15}N labeled choline in the rat brain

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Introduction:

The increase of total choline in tumors has become an important biomarker in cancer diagnosis. Choline (Cho) and choline metabolites can be measured in vivo and in vitro using multinuclear MRS. The recently developed hyperpolarization technique based on dynamic nuclear polarization opened new perspectives for metabolic studies using heteronuclei, since the NMR signal-to-noise ratio (SNR) is enhanced by up to four orders of magnitude (1). It has been recently shown that with an appropriate infusion protocol it is feasible to inject and detect hyperpolarized ^{15}N Cho in the rat head (2). The relatively long in vitro (2-4) and in vivo (2) characteristic decay time combined with the ability to observe hyperpolarized ^{15}N Cho in vivo makes this compound attractive for potential early detection of tumors. Since the previous pulse acquire in vivo study (2) did not allow to unambiguously conclude on the origin of the ^{15}N Cho signal (blood vs brain tissue), in the present study we designed a protocol to investigate the spatial origin of hyperpolarized ^{15}N Cho signal in the rat brain by selectively acquiring localized spectra from different spatial locations in the brain.

Methods:

All the in vivo ^{15}N MRS data were acquired on a 9.4T system (Varian/Magnex Scientific) using a home-built quadrature ^1H coil with a single 5-loop 10 mm ^{15}N coil placed on the head of the animal. Male Sprague-Dawley rats (~350g, n=6) were anesthetized using 1.5% isoflurane and a femoral vein was catheterized for infusing hyperpolarized ^{15}N Cho solutions. Respiration rate and temperature were maintained within normal range. 2.5M ^{15}N choline chloride (Sigma Aldrich) solutions in deuterated water-glycerol solvent doped with 50mM TEMPO free radical was polarized at 5 T and 1.05±0.05 K using a polarizer described in (5). After dissolution into 5 ml of D_2O , the ^{15}N Cho chloride sample was automatically transferred to a custom designed separator/infusion pump placed in the bore of the 9.4T system within 2s. 2.5 ml of the sample was infused over 9s into the rat femoral vein. The concentration of the ^{15}N Cho infusate was ~90mM. The injection was repeated twice on the same animal. The in vivo localized ^{15}N MRS acquisitions were performed using the SIRENE sequence (6). Two different voxel sizes ($5\times 8\times 8\text{mm}^3$ (n=5) and $3\times 4\times 6\text{mm}^3$ (n=2)) were selected in order to eliminate as well as possible the contribution of the major blood vessels. Excitation was performed using a 3ms 30° BIR4 pulse with 2s interpulse delay. The FIDs were analyzed with AMARES (7).

Results and Discussions:

The solid state ^{15}N polarization reached about 5% and the maximum polarization was obtained after ~3.5hours.

After FASTMAP shimming, the typical in vivo localized ^{15}N Cho linewidth was 6 Hz (Fig 2b). Fig. 1 displays a representative in vivo hyperpolarized ^{15}N Cho decay curve acquired in the rat brain using a voxel size of $5\times 8\times 8\text{mm}^3$ while eliminating the dorsal sagittal vein. As can be seen, the in vivo ^{15}N Cho signal was discernible above the noise level for about the first ~120 s. In order to further eliminate the contribution of blood vessels, in vivo acquisitions were performed in a smaller voxel size $3\times 4\times 6\text{mm}^3$ (Fig. 2). In this case, the in vivo ^{15}N Cho signal was also visible above the noise level for about the first ~70 s, as expected a lower SNR was obtained due to the smaller voxel size. It is interesting to note that similar to the in vivo pulse acquired experiment (2), the in vivo localized characteristic time decay exhibited a deviation from the mono-exponential decay with a very fast decay (11 ± 5 s) during the first seconds followed by a slower decay afterwards (83 ± 12 s), consistent with the in vivo pulse acquired study (2). The bi-exponential decay could reflect different decay times of Cho in the blood and afterwards in the brain due to uptake. The contribution of the slower decay is proportional with what we would expect to have in the brain at an uptake of $70 \text{ nmol g}^{-1} \text{ of brain min}^{-1}$ (8). The localized data, where the contribution of major blood vessels could be considered negligible while the contribution of small capillaries is still present, can allow a more accurate estimation of brain tissue component.

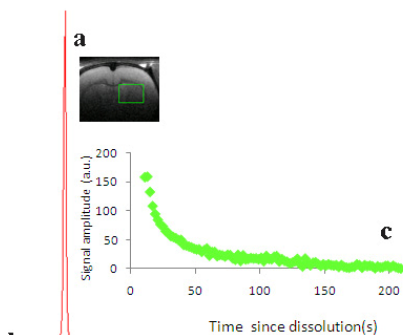


Fig 2: a) Coronal view of a rat brain showing the typical position of the voxel $3\times 4\times 6\text{mm}^3$; b) Plot of the first in vivo localized ^{15}N Cho spectra acquired in the same voxel, note the narrow linewidth; c) A representative hyperpolarized ^{15}N Cho in vivo decay curve acquired in the same voxel.

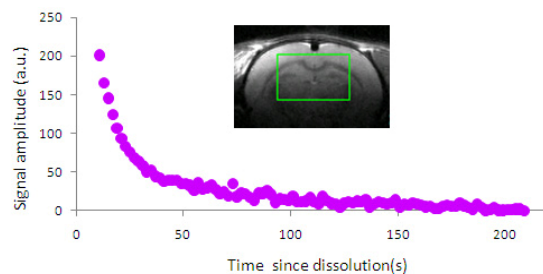


Fig 1: Coronal view of a rat brain showing the typical position of the voxel $5\times 8\times 8\text{mm}^3$ and a representative hyperpolarized ^{15}N Cho in vivo decay curve acquired in the same voxel.

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In the present study, we acquired localized in vivo hyperpolarized ^{15}N Cho spectra using two different voxel sizes in order to investigate the spatial origin of the ^{15}N Cho signal in the rat brain. In the small voxel where the major blood vessels contribution should be negligible, the in vivo ^{15}N Cho signal was visible for more than 1 min. This suggests that there is an important part of vivo hyperpolarized ^{15}N Cho signal that comes from brain tissue. To our knowledge the in vivo localized detection of hyperpolarized ^{15}N has not been demonstrated to date. In addition, the high SNR, the long characteristic time combined with the narrow localized ^{15}N Cho linewidth obtained in our in vivo study might allow the detection of phosphocholine, the product of choline metabolism (~ 0.2 ppm for phosphocholine vs choline). Moreover, the ability to observe localized hyperpolarized ^{15}N Cho in the rat brain makes this compound potentially useful for observing choline phospholipid metabolism in cancers.

References:

[1] J. H. Ardenkjaer-Larsen, et al., Proc Natl Acad Sci U S A, 2003;100:10158. [2] C Cudalbu et al., Phys Chem Chem Phys, 2010 ;12 :5818. [3] R. Sarkar et al., J Am Chem Soc, 2009;131:16014. [4] C. Gabellieri et al., J Am Chem Soc, 2008;130: 4598. [5] A. Comment et al., Conc Magn Reson Part B, 2007; 31B:255. [6] Choi IY et al., Magn Reson Med 2000 ;44 :387. [7] L. Vanhamme et. al., J. Magn. Reson. 1997; 129:35. [8] J. Klein et al., Neurochem Int, 1998;32:479.

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