In vivo detection of hyperpolarized 15N Choline in the rat

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Introduction:
15N MRS labeled experiments are especially useful for measuring the rates of synthesis and turnover of amino acids such as glutamate and glutamine, implicated in glutamate neurotransmission (1). However, the very low natural abundance of 15N (0.365%) makes the study of nitrogen metabolism difficult. A recent study has reported relatively long T1 for some nitrogen compounds (i.e. Choline) (2), suggesting that 15N may be a suitable candidate to be used with hyperpolarization by means of DNP (3). This is of special interest for observing phospholipid metabolism in cancer due to changes in choline metabolism (2). The aim of the present study was to demonstrate the feasibility of detecting hyperpolarized 15N labeled Choline in vivo in the rat.

Methods:
All the 15N 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 15N coil placed on the head of the animal. For the in vivo experiments, male Sprague-Dawley rats (~350g) 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. 15N choline chloride (Sigma Aldrich) solution, prepared at a concentration of 6M in a deuterated water-glycerol solvent doped with 50mM of TEMPO as free radical, was polarized at 3.35 T and 1.2 K using a polarizer described in (4). After dissolution into 5 ml of D2O, the 15N Cho chloride sample was automatically transferred to a phase separator placed in the bore of the 9.4T system within 6s. An external pump then injected 2.5 ml of the sample over 8s into the rat femoral vein. The concentration of the 15N Cho infusate was ~ 90mM. The injection was repeated two times on the same animal. The in vitro and in vivo acquisitions were performed using a 3ms 10° BIR4 pulse with 3s interpulse delay. The FIDs were analyzed with AMARES (5).

Results and Discussions:
The polarization in the cryostat reached 4% (corresponding to ~10000 times amplification compared to room temperature polarization at 9.4T). The maximum polarization was obtained after ~2hours, within 1600 s time constant. In vivo 15N Cho was discernible above the noise level for about the first ~90 s (Figure 1, 2) and the linewidth was 9 Hz. The fit for the in vivo 15N Cho T1 estimation was performed on the last part of the time course shown in Figure 1, from 27 to 105 s. Taking into account the RF flip angle correction, the T1 was estimated to be approximately 150 s in vitro and around 1min in vivo. The in vitro results on phantom were in agreement with the one in vitro study using 15N hyperpolarized Cho (2). The long T1 combined with the potential to observe hyperpolarized 15N Cho in vivo makes this compound useful for early detection of tumors and also for a potential utilization in the assessment of blood flow. The relatively long T1 of the nitrogen atom may render other nitrogen compounds suitable for DNP studies such as this one. To our knowledge the in vivo detection of hyperpolarized 15N has not been demonstrated to date. We conclude that it is feasible to detect hyperpolarized 15N in live animals.

References:

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