Determination of Diffusive and Transport Processes of Hyperpolarized [1,1,2,2-D_4, 1-^{13}C]-Choline in the Rat Kidney

Trevor P. Wade[1,2], Lanette Friesen-Waldner[2], Curtis N. Wiens[3], Kevin J. Sinclair[2], Rachel Katz-Brull[4,5], and Charles A. McKenzie[1,2]

[1]Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada, [2]Medical Biophysics, The University of Western Ontario, London, Ontario, Canada, [3]Radiology, University of Wisconsin, Madison, WI, United States, [4]Radiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [5]BrainWatch Ltd., Tel-Aviv, Israel

Target Audience: Scientists interested in renal uptake of choline.

Introduction: Choline is important in cell cycle progression, proliferation, and apoptosis, processes that are disturbed in malignant cells and tumours[1], so there is interest in developing an MRI choline molecular probe. It has been shown that [1,1,2,2-D_4,1-^{13}C]choline chloride (CMP1, or choline molecular probe 1) can be hyperpolarised and imaged *in vivo* by MRI[2], but cellular uptake of CMP1 has not been verified.

Purpose: To determine if the uptake of hyperpolarized CMP1 in rat kidneys is due to a saturable cellular transport process or an extracellular diffusion process.

Methods: *Hyperpolarization:* Male Sprague-Dawley rats (N=2) were anaesthetized using isoflurane and were scanned under a protocol approved by the institution's Animal Use Subcommittee. Animals were given atropine intravenously (1mg/kg) to avoid adverse cholinergic effects. 27.3mg (0.189mmol) CMP1 was mixed with 7.1mg of an aqueous solution of OX063 (61mM) and ProHance (2.9mM). The DNP sample was hyperpolarized in a DNP polarizer (HyperSense, Oxford Instruments, Abingdon, UK) at 1.4K, 94.1GHz, and 50mW. A volume of 2.5mL of this solution was injected over 12s into the tail vein at a final concentration of 20, 30, 40, or 50 mg/kg. Data acquisition started at the beginning of the bolus injection and was repeated every 4s to 60s. *Imaging:* Previous dynamic imaging experiments[2] indicated that in the timeframe of interest, ^{13}C signal was confined to the kidneys and aorta/vena-cava. To acquire high temporal resolution of the uptake kinetics, a 2 cm oblique axial slab was excited including both kidneys and excluding liver. The resulting slab was then frequency (but not phase) encoded (FOV 20cm, BW ± 2 kHz, 64 pixels, 3.1 mm resolution) resulting in a 1-D projection through both kidneys, with a repetition time of 4 s and flip angle of 10°.

Results & Discussion: Figure 1 indicates the axial slab that was excited to include both kidneys. With the frequency encode direction set L/R, it is possible to localize the signal in the slab to either the central vasculature (the central peak) or the kidneys (lobes on either side) (Stacked plot, Figure 2). From this, there is a clear vascular phase with the bolus becoming apparent at 4s and largely washing out of the vasculature by 24s. The signal in the kidneys starts to become apparent at 16 seconds and then peaks around 24s, and appears to stay in the kidneys out to at least 44s. If CMP1 uptake in kidneys was due solely to diffusion, the kidney signal would increase linearly with concentration. Instead, it began to plateau at doses above 30 mg/kg. This implies a saturable transport process is occurring, and uptake is not limited to diffusion.

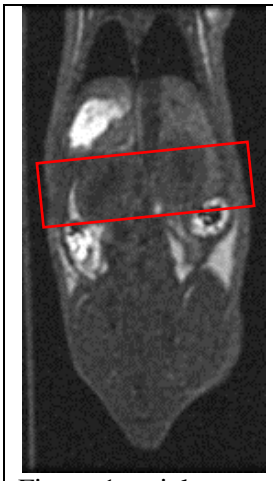

Figure 1: axial oblique slab over kidneys

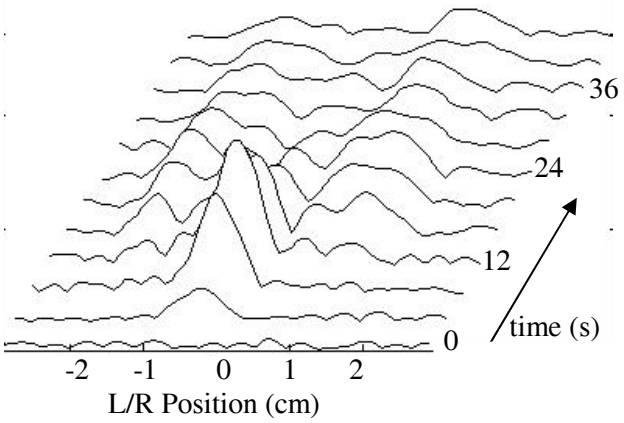

Figure 2: Dynamic 1D projections of the slab. The central peak is the signal from the vasculature, the lobes on either side represent the signal in kidney.

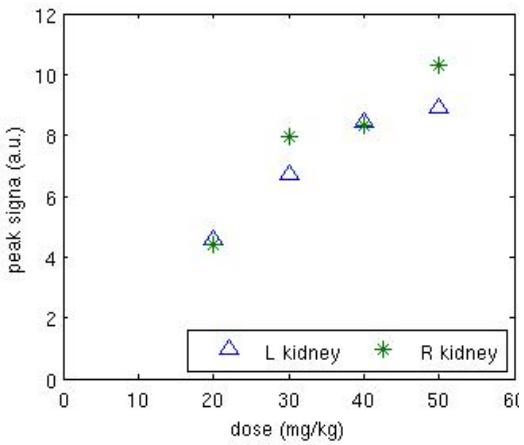

Figure 3: Peak signal as a function of dose for each of the compartments.

Conclusion: Uptake of CMP1 into rat kidneys in not limited to a diffusion process; rather, a saturable transport process occurs.

References: (1) Ridgeway. Crit Rev Biochem Mol Biol 2013; 48(1); 20. (2) Wade et. al., Proc ISMRM 2012 #269

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