Using Creatine and Phosphocreatine Infusions to Monitor Kidney Injuries

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Introduction

MRI is an excellent imaging modality for soft tissue contrast and can provide unprecedented information of deep soft tissue like the kidneys. Here, we aim to assess whether performing chemical exchange saturation transfer (CEST) [1] MRI of the kidneys after intra venous administration of creatine (Cre) or phosphocreatine (PCr) could be used to measure glomerulus filtration rate (GFR) in healthy and diseased kidneys. At ultra-high fields, we can, due to increased spectral separation and signal-to-noise ratio [2] detect Cre (2 ppm) and PCr (2.64 ppm) with higher sensitivity. Administration of exogenous Cre should allow for specific detection of Cre metabolism through temporarily elevating the concentrations of the various compounds involved.

Experimental

Naïve mice weighing 30-35 gr were used for all experiments. For IV injection of 350 mM Cre and PCr at neutral pH, a micro cannula was inserted in the lateral tail vein. All imaging was performed at the 21.1 T magnet at the NHMFL. A modified turbo spin echo sequence was used for all CEST acquisitions and each offset was acquired in one-shot using 8 s as the length of the repetition time. One 1-mm thick axial slice was placed to bisect the centers of the Major Calyces on both kidneys. CEST were performed by repeating (85 times) nine off-resonant pulses. This oversampling approach allows for correction of motion artifacts during the 1h 40 min scan. The saturation preparation consisted of 15 pulses, each 200 ms long with block-pulse shape (bp) and B_1 = 2.5 μT resulting in a 3 s saturation pulse train. Injection of the respective compound occurred at 8 min following start of the acquisition. Data were processed in Matlab for visualization of the dynamic CEST contrast.

Results and Discussion

First we compared the Z-spectra for Cre and PCr in phantoms with similar acquisition methods that we would use *in vivo*. Fig. 1 show that both metabolites are well detected at 50 mM, with stronger contrast seen for Cre which peaks at 2.0 ppm and weaker contrast for PCr with a maximum at 2.6 ppm. The differences in contrast are due to both number of labile protons per molecule (Cre = 4, PCr = 2) and exchange rates (Cre k_{sw} = 950 s^{-1}, PCR k_{sw} = 140 s^{-1}). Unfortunately, while Cre displays better contrast, the solubility of this metabolite was a problem for testing *in vivo*. PCr was easier to dissolve in DI water, reaching 350 mM at room temperature. After injecting PCr into mice, ~3 % contrast is seen in the kidneys with this contrast peaking at ~ 40 minutes after injection (Fig. 2).

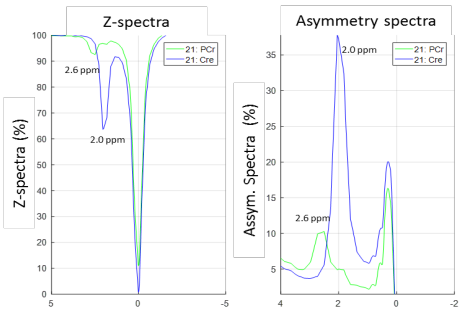

Fig.1 Traditional CEST Z-spectra and MTR_{asym} spectra for Cre and PCr.

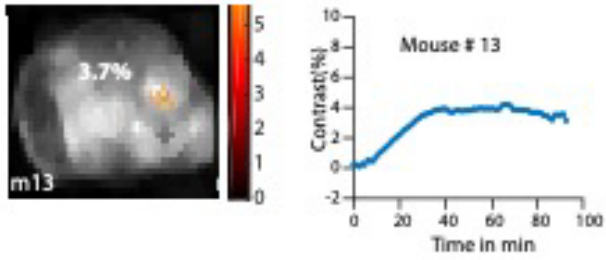

Fig.2 In vivo CEST imaging results after PCr injection. The left panel shows the contrast in the kidney at 2.6 ppm at ~ 60 min after injection and the right panel shows the contrast in the kidneys as a function of time.

Conclusions

Our initial data show that CEST contrast can be used to differentiate between Cre and PCr *in vitro* at 21.1 T. CEST contrast can also be readily detected *in vivo* in the kidneys after injection of PCr. Due to solubility issues, *in vivo* data show weak contrast for Cre (<1.5 % on average) while injection of 350 mM PCr produces ~3 % contrast. Work is underway to further analyze the data and try to use our CEST spectra to separately determine uptake of PCr and Cre in the kidneys after injection of PCr for evaluating kidney function.

Acknowledgements

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References

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[2] Roussel, T., *et al.,* NMR biomed, **31**, e3995 (2018).