Assessing water influx and retention in the brain of AQP4 knockout mice by ^{17}O-MRI

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Target Audience: Researchers in cerebral blood flow & metabolism; researchers in hetero-nuclei chemical shift imaging

Introduction

Aquaporin-4 (AQP4) is thought to be the primary mediator of water exchange between the blood and brain tissue[1]. This conclusion is based on its unprecedented level of expression in astrocyte endfeet that surround vascular endothelial cells at the blood brain barrier, and the ability of AQP4 knockout mice to resist CNS insults that lead to the accumulation of water in brain tissue, i.e., cerebral edema. However, until recently a direct *in vivo* measure of AQP4-mediated blood-brain water permeability has not been attempted. ^{17}O MRI allows *in vivo* quantification of cerebral metabolism, blood flow, and water exchange between different tissue compartments, e.g., brain tissue and ventricles[2]. Due to the low natural abundance of ^{17}O, current ^{17}O MRI methods rely on large number of signal averages, resulting in limited spatiotemporal resolution. In this study, we used a keyhole acquisition strategy[2] for accelerated ^{17}O chemical shift imaging (CSI). This approach was used to delineate the kinetics of $H_2{}^{17}O$ uptake and washout in both brain tissue and ventricles of AQP4 knockout and wildtype mice.

Methods

AQP4 knockout mice (AQP4-KO, n=4) and their wildtype littermates (WT, n=6), age two months, were scanned on a 9.4T Bruker Biospec MRI scanner. Anesthesia was maintained by mixing 0.5-1% isoflurane with 30% O_2 and 70% N_2. A 30G catheter inserted into the tail vein was used to inject 150 µL saline enriched to 12.6% $H_2{}^{17}O$ over 25-30 seconds.

The ^{17}O-CSI data were acquired with a custom-built, 2.5-cm surface coil. At baseline, a fully sampled 3D ^{17}O CSI dataset was acquired with the following parameters: TE/TR, 0.64/12.5 ms; matrix size: 9x9x5 pixels; spectral width, 30 kHz; FOV, 2x2x1.5 cm^3; NAV, 128. Total scan time was 10.8 minutes. During and after the $H_2{}^{17}O$ injection, a keyhole ^{17}O-CSI acquisition (central 3x3x3 phase encodes) was acquired dynamically to improve the temporal resolution (340 ms scan time per dataset)[3]. A total of 3300 keyhole datasets were acquired over 3 minutes before and 15.5 minutes after the $H_2{}^{17}O$ injection.

For data reconstruction, composite CSI datasets were generated by replacing the central k-space of the fully sampled CSI dataset with the keyhole data. To improve the signal-to-noise ratio, the keyhole dataset was binned to 206 frames with 16 averages for each frame, yielding a temporal resolution of 5.4 seconds. A 100 Hz line-broadening was applied to the FIDs and the k-space data with were zero-padded to yield a matrix size of 18x18x5. From the Fourier transformed CSI data, the kinetics of $H_2{}^{17}O$ accumulation was quantified in both the brain tissue and the CSF. A mono-exponential function was fit to the washout part of the normalized $H_2{}^{17}O$ curves to yield peak and steady-state $H_2{}^{17}O$ uptake and the time constant of $H_2{}^{17}O$ washout.

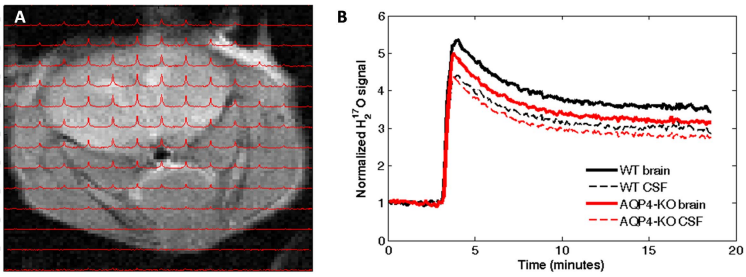

Figure 1. A. ^{17}O CSI overlaid on ^{1}H image. **B**. Normalized time course of ^{17}O signal in brain and CSF.

Results

Fig. 1 shows representative ^{17}O-CSI data and dynamically ^{17}O signal profiles in brain and CSF. As expected, ^{17}O signal increased rapidly following the injection of $H_2{}^{17}O$ and reached a peak level nearly coincident with the end of the infusion. Compared to wildtype controls, AQP4-KO mice showed a trend toward lower peak and steady-state levels of $H_2{}^{17}O$. The time constant of $H_2{}^{17}O$ washout was similar for both groups of mice. In WT mice, image voxels that comprised of brain tissue only showed significantly higher steady-state $H_2{}^{17}O$ level compared to those voxels that are primarily CSF. AQP4-KO mice also showed a trend of increased steady-state $H_2{}^{17}O$ level in the brain; however, no statistical significance was detected.

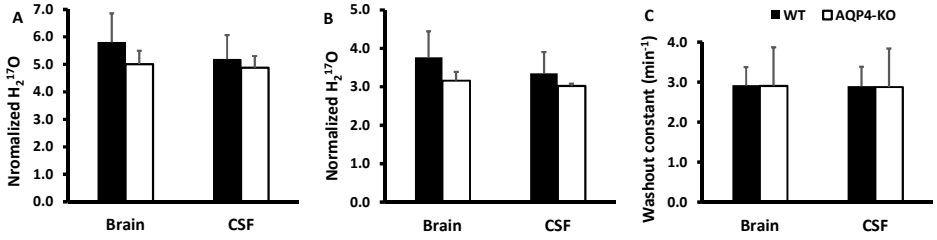

Figure 2. Peak (A) and steady-state (B) $H_2{}^{17}O$ uptake and the time constant of $H_2{}^{17}O$ washout (C).

Conclusion

In the current study, we implemented a keyhole ^{17}O-CSI acquisition strategy with high temporal resolution. Our results suggest decreased water uptake and retention in AQP4-KO mice, consistent with previous findings and supporting the model that AQP4 plays a significant role in water movement into the brain[4]. Further, similar $H_2{}^{17}O$ washout rates suggest that cerebral blood flow is unaltered in AQP4-KO mice.

References

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