The effect of aquaporin-4 inhibition on cerebrospinal fluid-tissue water exchange in mouse brain detected by magnetization transfer indirect spin labeling MRI

Zilin Chen[1#], Joseph H. C. Lai[1#], Jiadi Xu[2,3], Jianpan Huang[4*], Kannie W. Y. Chan[1,3,5-7*]

[1]Department of Biomedical Engineering, City University of Hong Kong, Hong Kong, China; [2]F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Research Institute, Baltimore, MD, USA; [3]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong, China; [5]Hong Kong Centre for Cerebro-Cardiovascular Health Engineering (COCHE), Hong Kong, China; [6]Tung Biomedical Sciences Centre (TBSC), Hong Kong, China; [7]City University of Hong Kong Shenzhen Research Institute, Shenzhen, China. [#]Authors contributed equally

INTRODUCTION: The exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) within brain tissue facilitates waste clearance as a drainage pathway[1,2]. Aquaporin-4 (AQP4), the primary water channel for water transport, contributes to this clearance system[3]. Imaging the water exchange between CSF and brain tissue using MRI is still a challenge as this process is relatively slow compared to the bulk flow inside the ventricles. Magnetization transfer indirect spin labeling (MISL) MRI, first saturates the water molecules in the brain tissue using magnetization transfer (MT) labeling and then images the CSF to quantify the CSF-tissue water exchange in an indirect way[4]. Yet, so the sensitivity of MISL at clinical-field-strength MRI (≤3T) remains unknown. Here, we optimized the parameters at 3T and applied the optimized MISL to monitor the hampered water exchange between CSF and brain tissue in the presence of AQP4 inhibition.

METHODS: MRI experiments were performed on a horizontal bore 3 T Bruker BioSpec system (Bruker, Ettlingen, Germany). Saturation frequency offset and saturation power were optimized in vitro using a water phantom, and in vivo using C57BL/6 mice with CSF and brain tissue. For AQP4 inhibition, a bolus of 20 mg/ml TGN-020 at a dosage of 200-mg/kg[5] was intraperitoneally injected into the mouse body over one min using an MRI-compatible syringe pump (Harvard Apparatus, US). Mice from the control group followed the same injection protocol but with saline.

RESULTS: We used MISL with optimized parameters, i.e. saturation frequency offset = −10 ppm, B_1 = 2 μT, TE = 250 ms, to image the effect of AQP4 inhibitor TGN-020 on mouse brain. An obvious trend of MISL signal suppression was observed after TGN-020 administration (Figure 1A-C). The MISL signal gradually declined and became steady after half an hour. The suppression persisted up to 60 min within the monitored period. With reference to the baseline, the MISL signal was substantially reduced by 15.2%±5.5% at 28 min and by 14.7%±9.1% at 60 min in TGN-020 group, which were significantly lower than that of saline group (Figure 5B, P = 0.0169 at 28 min and P = 0.0178 at 60 min). On the contrary, the MISL remained stable after saline injection, supporting that the decrease in TGN-020 group was due to the AQP4 inhibition. In terms of MT, no substantial change was observed after TGN-020 or saline injection, which was reasonable as the short-term AQP4 inhibition was not expected to change the macromolecule level in brain tissue.

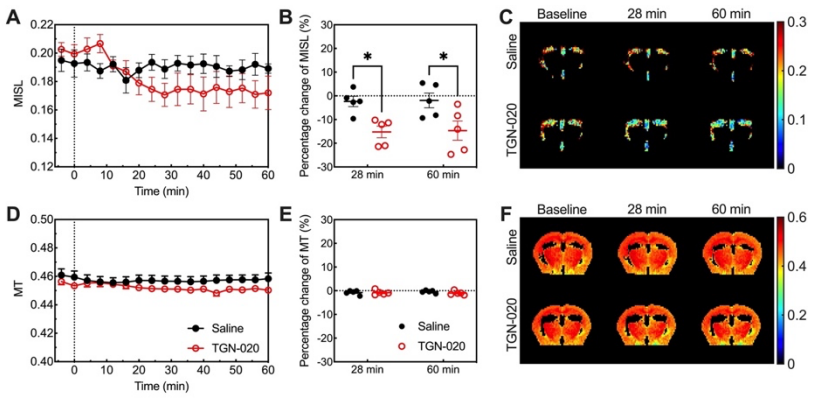

Figure 1. (A, D) The dynamic changes of MISL and MT respectively. (B, E) The percentage changes of signal with respect to baseline after TGN-020/saline administration at 28 and 60 minutes for MISL and MT. (C, F) Representative maps of MISL and MT. Multiple t-test (n=5), * P < 0.05.

DISCUSSION: We presented the optimization and application of noninvasive MISL to assess water exchange in mouse brain at a preclinical 3T MRI system, provide supplementary information to the previous study performed at 11.7T[4]. Although the MISL signal in CSF is majorly originated from MT signal in brain tissue after water exchange, we did not observe a significant change in MT (Figure 1D-F), suggesting the significant MISL change (Figure 1A-C) was not a result of MT but rather due to AQP4 inhibition and MISL can effectively indicate the AQP4-related events in the brain

CONCLUSION: Our MISL study performed at 3T scanner provided information about optimized parameters for assessing water exchange in mouse CSF and showed its potential in evaluating meningeal lymphatic function under AQP4 inhibition, highlighting the possibility clinically translating MISL to offer valuable information on water transport for diagnosis and prognosis for neurodegenerative diseases.

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