

PHARMACOLOGICAL MRI BY DYNAMIC CEST IMAGING

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Introduction

In pharmacological MRI (phMRI), MR indices such as BOLD and CBV were widely employed to investigate the effect of pharmaceutical compounds on hemodynamic behavior. [1] These evaluations indirectly reflect physiological tissue response of drugs since cerebral activity will increase vascular nutrition supply. Recently, a novel imaging technique termed chemical exchange saturation transfer (CEST) is capable of *in vivo* pH detection and molecular imaging. Inherent amide proton with chemical shift among 2~5ppm has been reported to be sensitive to pH value. [2, 3] In this study we propose to utilize dynamic amide proton transfer (APT) CEST imaging for observation of pharmacological effects of methamphetamine (mAMPH) on a normal rat model.

Materials and Methods

Adult male Sprague-Dawley rats (280~340g, N=5) were scanned under anesthesia with 1.5% isoflurane. Five z-spectra were acquired successively as baseline before an intravenous tail-vein 3mg/kg mAMPH injection; followed by twenty-three post injection z-spectra. All experiments were carried out at a 4.7 T Bruker Biospec 47/70 spectrometer with a volume coil for transmitting and a surface coil for receiving. Fastmap was used to reduce the field inhomogeneity, and the central frequency of water was carefully adjusted. A 4 sec continuous wave (CW) RF with power of 1.25uT was designed for magnetization saturation and followed by a spin-echo EPI for imaging. The imaging parameters were set as below: TE/TR=45/11500ms, matrix size=64x64, FOV=3.2cm, slice thickness=2mm. The off-resonance frequencies of CEST RF swept from +400 to -400Hz with an interval of 100Hz. The MTR_{asym} time course was then evaluated by MATLAB scripts. The MTR_{asym} was calculated by $(S_{\text{off}} - S_{\text{on}})/S_0 \times 100\%$, where S_{on} , S_{off} and S_0 represent +400Hz CEST image, -400Hz CEST image and image without CEST RF, respectively. The mean of 5 baseline points of MTR_{asym} time courses were shifted to zero. A model free method, temporal cluster analysis (TCA) [4], was performed to check the changes. The minimum location of MTR_{asym} time course was calculated pixel by pixel in the region of interest.

Results

Fig. 1 shows the averaged whole-brain MTR_{asym} time course at 2ppm of 5 rats. It is noted that MTR_{asym} value has about 0.25% drop after the injection of amphetamine, and then the signal recovery trend was observable after minimum signal had achieved. Signal reduction of MTR_{asym} in APT could be referred to the decrease of tissue pH value or amide proton concentration. The same phenomenon also appeared in the TCA results of whole brain in Fig. 2. The mAMPH injection at 10th min led to an increase of the count number of minimum, indicating that minimum value of MTR_{asym} happened most frequent among 2~14 min after injection. The second group of increase was about 22~34 min after injection corresponded with Fig. 1, where there was a drop near 40 min. In Fig. 3, mean MTR_{asym} time courses of cortex and striatum of 5 rats were shown. It was noted that the signal drop of cortex was about 1%, however, the signal at striatum revealed an increasing trend about 0.3%.

This contrary result represented that there was an opposite response of amphetamine between cortex and striatum. Assuming consistent amide proton concentration during the whole session, the pH value was speculated to decrease in the cortex area during mAMPH challenge. On the other hand, the pH value might slightly increase in striatum. Fig. 4 shows the MTR_{asym} difference map evaluated by subtracting baseline and minimum MTR_{asym}. It also demonstrated that the region of cortex held more negative value and striatum positive value, suggesting the same result as in Fig. 3.

Discussion and Conclusion

Conventional contrast source of phMRI are CBV and BOLD, which represent hemodynamic response in brain. In this preliminary research, APT CEST contrast was first shown to provide additional information of the chemical micro-environment during drug challenge. Different responses of mAMPH were discovered between cortex and striatum. The underlying mechanism still need for further investigation. Since APT signal is small and easy to be altered, it should be optimized utilizing special modified sequence or analytical methods. Besides, more studies should be carried out to identify the pharmacological effect of different frequency offset. In conclusion, we have demonstrated that drug effect is observable through APT CEST. It could be a powerful indicator for imaging localized *in vivo* chemical response by pharmacological compounds.

References

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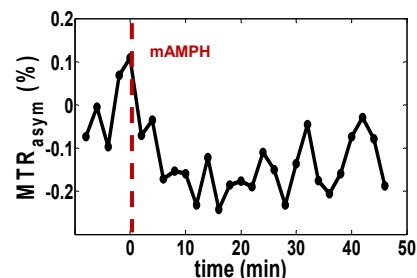


Fig. 1 Whole-brain MTR_{asym} time course at 2ppm (N=5). Note the signal reduction after injection.

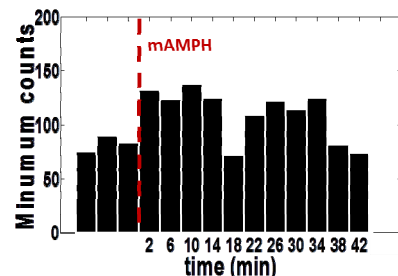


Fig. 2 TCA of 5rats. Minimum counts rose up after injection.

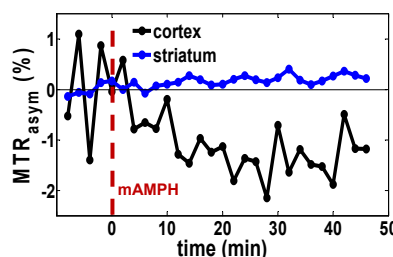


Fig. 3 MTR_{asym} time course of cortex (black) and striatum (blue). There was an opposite response between cortex and striatum.

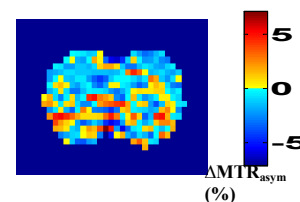


Fig. 4 Difference map between baseline and minimum one. Amphetamine caused different effects on cortex and striatum region.