MRI of neuronal recovery after methamphetamine treatment of traumatic brain injure in rats

Guangliang Ding[1], Michael Chopp[1,2], David J. Poulsen[3], Lian Li[1], Changsheng Qu[4], Qingjiang Li[1], Siamak P. Nejad-Davarani[1], John Budaj[1,5], Hongtao Wu[4], Asim Mahmood[4], and Quan Jiang[1]

[1]*Neurology, Henry Ford Hospital, Detroit, Michigan, United States,* [2]*Physics, Oakland University, Rochester, Michigan, United States,* [3]*Biomedical and Pharmaceutical Sciences, University of Montana, Missoula, Montana, United States,* [4]*Neurosurgery, Henry Ford Hospital, Detroit, Michigan, United States,* [5]*Biomedical Engineering, Oakland University, Rochester, Michigan, United States*

Introduction Traumatic brain injury (TBI) is a leading factor for morbidity and mortality in Western countries[1] and there is an urgent need to develop a novel approachs for the treatment of TBI. Methamphetamine has been shown to decrease cell death and improve functional outcomes in ischemic stroke. Stroke and TBI share many common pathophysiological pathways and thus, in this study we assessed the effects of methamphetamine on brain tissue and functional recovery following TBI in rats and employed MRI, immunohistology, and neurological functional tests as outcome measures.

Materials and Methods Young male Wistar rats were anesthetized with chloral hydrate (350 mg/kg) and injury was induced by a pneumatic impact device on the intact dura. A single strike was delivered at 4 m/sec and a 2.5 mm of compression to the left cortex with a pneumatic piston containing a 6mm-diameter tip. One group of rats, referred to as, the treated group (n=10), were treated at eight hours after the TBI with a bolus dose of 0.42 mg/kg methamphetamine via the saphenous vein followed by continuous infusion intravenously (IV) with 0.05 mg/kg/hr for 24 hrs. Animals, assigned as to the control group (n=10), received the same volume of saline as bolus IV dose followed by continuous IV infusion with 6.6 µl/hr for 24 hrs. MRI measurements, including T_2-weighted imaging (T2WI), susceptibility weighted imaging (SWI), and diffusion tensor imaging (DTI),.were performed with ClinScan 7T system. A birdcage coil was used as transmitter and a quadrature half-volume coil as receiver. MRI scans were performed one day before TBI, and at 1 and 3 days post TBI and then weekly for 6 weeks. Neurological function was monitored by modified neurological severity scores (mNSS) and foot-fault test post brain injury. Using light microscopy and laser scanning confocal microscopy, we measured Bielshowsky's silver and Luxol fast blue (BLFB) immunoreactive staining as an index of axonal and myelin damage, respectively. Lesion volumes were measured with hematoxylin and eosin (H&E) immunohistochemistry. Two MRI regions of interest (ROI) were identified as the TBI core and recovery areas, respectively, for analysis of MRI parameters. The first ROI, referred as the TBI core, was demarcated on T_2 map obtained 6 weeks after TBI, by using the T_2 value threshold of mean plus two standard deviations based on the T_2 value measured in the pre-TBI T_2 map for each animal. The second ROI, referred as the TBI recovery area, was demarcated by subtracting the TBI core from the TBI lesion area in T_2 maps obtained 24 hrs after TBI. Q-ball based DTI was performed using ex vivo MRI scans. For the q-ball imaging, b = 900 s/mm^2 at 128 directions was applied. Diffusion standard deviation (SD) map, derived from q-ball imaging, was created based on calculating the deviation of diffusivity from a sphere for each voxel in the image[2]. If diffusion is constrained by tubular structures, the SD will possess a non-zero value based on the complexity of the structure.

Results The lesion volumes of TBI damaged cerebral tissue were demarcated by elevated values in T_2 maps and measured at 24 hrs, 72 hrs and weekly from 1 to 6 weeks post-TBI in rats (Fig.1 a). There was no therapeutic effect ($p > 0.41$) on lesion volumes during 6 weeks after TBI in rats. With H&E slices, lesion volumes were histologically measured as 10.4±4.8% for the treated rats and 14.3± 5.2% for the controls, no statistically significant differences were detected between the two groups. The temporal profiles of fractional anisotropy (FA) values, normalized to pre-TBI measurements, in the TBI core and recovery ROIs were calculated (Fig.1 b). The values obtained from the TBI core ROIs remained low within six weeks after TBI for both control and treated groups, and no significant differences of FA measurements were detected in the core regions between the two groups. Treatment significantly increased FA values in the TBI recovery ROIs compared with control group at 5 and 6 weeks after TBI (Fig.1 b). Significant correlation was detected between normalized FA and BLFB measures in TBI recovery ROI ($R=0.54$, $p<0.02$). Histologically measured axons and myelin using BLFB also exhibited a significant increase ($p<0.001$) in treated group (25.84±1.41%) compared with control group (17.05±2.95%). Methamphetamine treatment significantly improved mNSS at 2 to 6 weeks ($p < 0.05$), and foot-fault tests from 3 days to 6 weeks ($p < 0.05$) in rats after TBI.

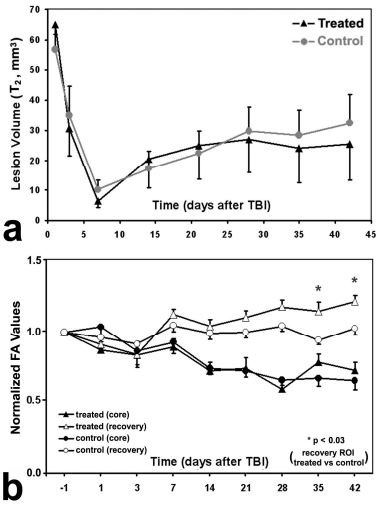

Fig.1 MRI lesion volumes measured from T_2 map (a) and FA values (b).

Discussion The effects of the methamphetamine treatment in rat are dose and time dependent[3]. In this TBI study, the methamphetamine treatment did not reduce lesion volume after TBI, consistent with histological H&E measurements in this study. However, improved FA, axonal reorganization, and functional recovery suggested that this treatment initiated at 8 hours post TBI was neurorestorative. MRI FA was able to monitor white matter recovery with well-organized axonal bundles, and similar results have been described for the detection of white matter recovery after treatment of stroke in rats[2]. The SD map from DTI is sensitive to early stages of white matter reorganization (more crossing fibers), and superior to FA in the detection of white matter reorganization with prominent crossing fiber[2]. An ex vivo scan, figure 2, demonstrated that SD and FA showed the same pattern. Thus, fiber crossing, at 6 weeks after TBI, was not a reason why FA values of TBI recovery cerebral tissue were lower in control rats than in the methamphetamine treated rats. Hence, high FA values in treated rats reflected improvement of white matter. With elevated values, both SD (Fig.2 b) and FA (Fig.2 a) maps detected the white matter fiber tract circled the lesion core. Fig.2 c, shows fiber orientation map derived from a q-ball MRI scan, which did not show much fiber crossing surrounding the TBI lesion core (see the enlarged part inside of blue frame, Fig.2 d). These data are consistent with the histological result using BLFB staining (Fig.2 f, enlarged of the red box from Fig.2 e). Thus, the evolution of FA measurements suggests that methamphetamine treatment of TBI improves white matter reorganization from 5 to 6 weeks after TBI in rat compared with saline treatment, and hence, the improved white matter may contribute to the functional outcomes after TBI in rat.

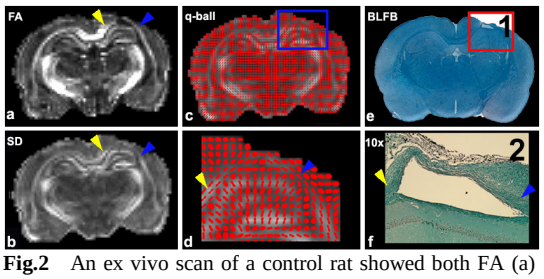

Fig.2 An ex vivo scan of a control rat showed both FA (a) and SD (b) detected axonal reorganization after TBI, q-ball map (c, d: enlarged the blue box in C) showed no much fiber crossing in high SD and FA areas. MRI results were consistent with BLFB slice (e, f: enlarged part).

References

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