

Pathological change in nigrostriatal pathway in MPTP induced Parkinson's disease animal model using DTI and MRS

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Synopsis

The differential diagnosis of parkinsonian disorders is a challenge for clinicians, especially during the early stages of disease. In present study, we evaluated the potential of long-term investigations of the MPTP induced neural degeneration mice model, using diffusion tensor imaging and magnetic resonance spectroscopy as early detection tools for pathophysiological changes in the nigrostriatal pathway.

Introduction

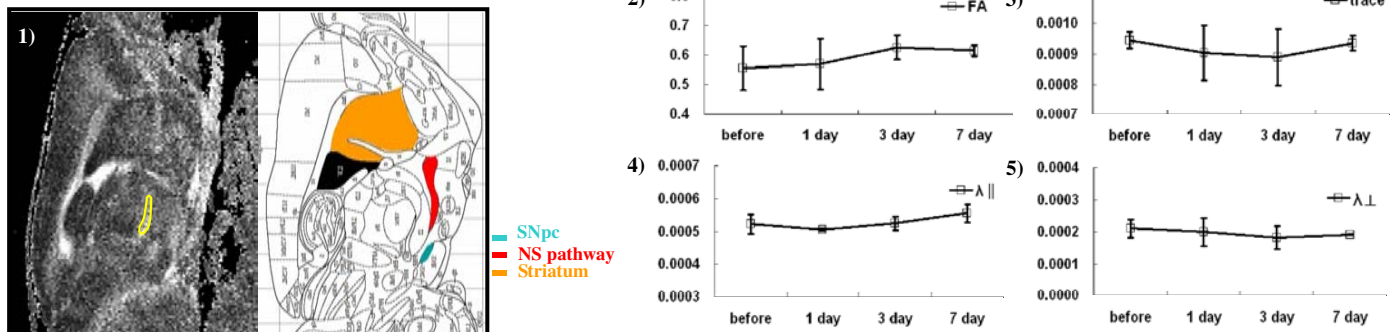
Parkinson's disease (PD) is a common chronically progressive neurodegenerative disease of the CNS characterized by tremors, rigidity, and bradykinesia. The clinical signs of PD appear only when striatal dopamine (DA) concentration is significantly decreased i.e., striatal DA is depleted 80%, and SNpc (Substantia Nigra pars compacta) DA neurons are degenerated 60–80%. C57BL/6 mouse strain is known to be highly susceptible to the neurotoxin – MPTP and have been widely used as an in vivo model to test therapeutic strategies in PD. In previous studies of animal models of PD by MRI, several techniques were employed: magnetic resonance spectroscopy (MRS)/MRSI which showed persistent reductions of striatal *N*-acetyl aspartate (NAA), and T2WI which observed a significant signal increase in the striatum generally associated with the presence of edema. In present study, high resolution DTI sensitive to the evaluation of the integrity white matter fiber tracts was employed to noninvasively quantify the integrity of myelin and axon within mice nigrostriatal pathway along with in vivo proton MRS in order to measure the biochemical changes in brain tissue after MPTP treatment.

Material & Methods

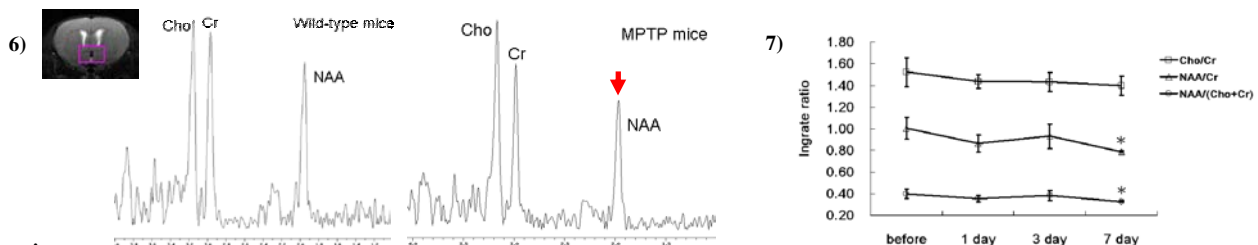
21 male C57BL/6J mice 16 weeks old were examined in the present study. The mice were divided into four groups of 3 each. Images were acquired before and at 1st, 3rd, 7th day after MPTP injection. MPTP with a dose of 20mg/kg was dissolved in saline (0.9% NaCl) and was administered four times intraperitoneally at 2h intervals. All data acquisition was performed in a 4.7T Biospec spectrometer (Bruker, Germany). For DTI data acquisition, a spin echo diffusion sequence with FOV=2 x 1.25 cm, TR=2000ms, TE=34.7ms, Matrix=256 x 160, Slth=0.8mm, b value=1000 s/mm², NEX=20, δ =7.5ms, Δ =16ms, and diffusion encoding directions=6 was used. The total scan time is 12hr 27min. For DTI data analysis, quantitative indices, including the analysis of diffusion trace (tr(D)), λ_{\parallel} , λ_{\perp} , fractional anisotropy (FA), were all calculated by an in-house program. ROI was manual defined by MR Vision. For MRS data acquisition, MRS was performed via the PRESS sequence with voxel size=3 x 2 x 3 mm³, TR=3500ms, TE=136ms, NEX=256, and total scan time= 13 min. The ROI was localized on striatum. MRS data analysis was performed by Bruker ParaVision software for the integral ratio of each spectrum. The mean and standard deviation of all the measurements were subjected to paired t tests for the variation between different days after MPTP injection. p<0.05 was considered as statistically significant.

Results

The pathological changes of the nigrostriatal pathway induced by MPTP are indicated as Fig.1. The mice brain atlas was used as the criterion to define the ROI of nigrostriatal pathway as shown in Fig. 1. The quantitative values obtained from DTI with the ROI selected as nigrostriatal pathway were illustrated in Fig. 2-5. The FA values was found to increase from the 1st day and decreased on 7th day after MPTP treatment, while the trace values was decreasing form 1st day and increased on the 7th day, which might indicate the neuronal changes in the white matter, and the trace λ_{\parallel} and λ_{\perp} values were the diffusivity parallel and perpendicular to the nigrostriatal pathway, respectively.



The MRS on the striatum prior to and after 7 days of MPTP treatment was shown in Fig. 6. The ratio of Cho/Cr, NAA/Cr and NAA/(Cho+Cr) were shown in Fig. 7. Neuronal marker, *N*-acetyl aspartate (NAA) peak decrease is apparent after MPTP treatment.



Discussion

MPTP mice had significantly FA decrease in the region between the substantia nigra and the lower part of the putamen/caudate complex, namely nigrostriatal pathway, which consist mainly of the nigrostriatal dopaminergic neurons. Early PD pathological change was observed in this region via DTI study. The finding might contribute to the early diagnosis of PD though the change is subtle and the pathological meaning is still unknown. MRS of MPTP-treated mice demonstrated significant *N*-acetyl aspartate (NAA) decrease in the striatum on the 7th day, which also provides another marker for the early diagnosis of PD.

References

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