MRI and MRS study of a transgenic mouse model of D1 dopamine receptor positive striatal cell depletion

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Introduction: Development of transgenic mouse models represents a major milestone in neurodegenerative disease research. We have created a transgenic mouse model with post-natal striatal D1 receptor positive (D1R+) cell loss [1] to mimic the human Parkinson-plus syndromes and Huntington's disease (HD). Transgenic mice survive for an extended period of time allowing us a significant experimental time window to elucidate the mechanisms of brain disorders characterized by striatal cell loss. Several MRS studies have shown the striatal impaired energy metabolism and neuronal dysfunction in HD mouse model [2,3] and human [4]. The purpose of this study was to investigate brain changes using MRI and MRS in a transgenic model of D1R+ cell depletion. T2-weighted RARE MRI and ^{1}H PRESS MRS were used to reveal anatomical changes and to monitor brain metabolism respectively.

Materials and Methods: Six D1R+ depletion transgenic mice and 5 littermate control wild-type mice (8-20 weeks), weighing 22-30g, were MRI scanned. The mice were anaesthetized with a 1-1.5% isoflurane-oxygen mixture (flow rate 1.0-1.5 liter/minute via a nose cone) and respiratory rate was monitored during the scan. All MRI measurements were performed on a Bruker Biospin 4.7T animal MRI scanner. A volume coil was used for excitation and a custom made surface coil was used for receive using a T2 weighted RARE sequence (TR 4000ms; echo train 8; effective TE 67ms; FOV 2.5cm; Matrix 256*256; slice thickness 0.5mm; slices 24 with no gap; NEX 16). The spectroscopic volume of interest (VOI 1.5*1.5*1.5mm^3) was placed in the striatum by visualization of the T2 images and excluded cerebrospinal fluid. The ^{1}H-MR spectra were acquired using a water-suppressed PRESS sequence (TR: 1000 ms; TE 136 ms; data points 1024; average 2048).

Results: Enlargement of the lateral ventricles was observed as well as striatal atrophy (Fig 1). The average lateral ventricular volume in the D1R+ ablation mutants was 2.63±0.44ul compared to 1.9±0.16 ul in the control mice. NMR spectra of D1R+ depletion mice (Fig2 a) and the control mice (Fig2 b) showed the main metabolic peaks. The ratios of these peaks in the transgenic group and control group showed significant differences (Table 1).

	NAA/Cr	Cho/Cr	Glx/Cr
D1R+ depletion mice	0.78±0.2	1.60±0.34	0.44±0.15
Wild-type mice	1.05±0.12	0.95±0.21	0.17±0.02
T-test(p value)	<0.1	<0.01	<0.01

Table 1 Relative metabolite ratios in D1 depletion mice and wild-type mice

Discussion and conclusion: The novel mouse model of D1R+ striatal cell ablation was characterized by significant weight loss, locomotor hyperactivity, seizures on handling and hindlimb dystonia on tail suspension. We have described a non-invasive method of investigating the neurodegenerative process *in vivo*. Our reults demonstrated remarkable metabolic changes in the striatum of the transgenic model with postnatal D1R+ cell loss. The reduction of NAA/Cr in the mice may reveal either the loss of the D1R+ neurons or dysfunction of the neurons. The increase of the Cho may reflect the astrogliosis and the increased GLx may reflect increases in glutamate release that is secondary to metabolic failure in the neurons affected by the diphtheria toxin expressed in the model[1]. The enlargement of the lateral ventricles is likely to be secondary to striatal atrophy (i.e. hydrocephalus *ex vacuo*) making it likely that the reduction of NAA/Cr in the mutants was probably due to cell loss.

Acknowledgements: Supported by NHMRC. **Reference:** [1] Drago J. *J Neuroscience* **18**: 9845-9857 (1998). [2] Jenkins B. G. *J Neurochem* **74**: 2108-2119 (2000). [3] Dellen A.V *Neuroreport* **17**:27 (2000). [4] Pernaute R. S. *Neurology.* **11**: 806-12 (1999).

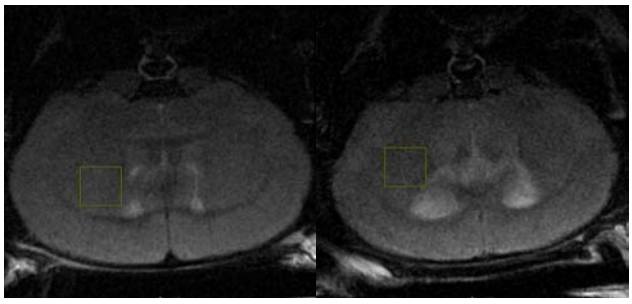

Fig 1: Typical T2-weighted brain coronal images of the wild-type mouse (left) and transgenic mouse(right). Enlargement of the ventricles is obvious in the transgenic mouse. The square ROI in each image represents the selected voxel in the striatum for the spectroscopic acquisition

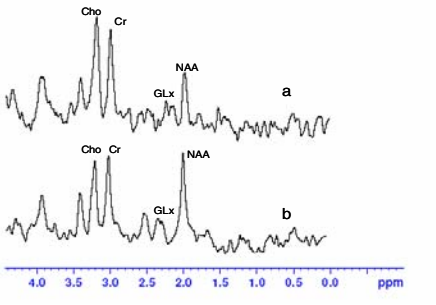

Fig 2: Typical striatal spectrum of D1 depletion mice (a) and wild-type mice (b).