Multimodal MRI of a novel transgenic model of Parkinson's Disease (MitoPark mice)

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Target Audience: Researcher in Parkinson's disease using MRI

PURPOSE: Parkinson's disease (PD), the second most prevalent neurodegenerative disorder [1], is characterized by a number of motor symptoms. MitoPark mouse is a relative new model of PD. It has dopamine-neuron specific inactivation of mitochondrial transcription factor A, a protein essential for mitochondrial DNA expression and maintenance, which renders respiratory chain deficient in dopamine neurons. [2]. MitoPark mouse exhibits several critical clinical features of PD, including progressive neurodegeneration and death of neurons, followed by motor dysfunction. The aim of this study was to apply MRI to investigate cerebral blood flow (CBF), apparent diffusion coefficient (ADC), and $T2^*$ changes in the caudate putamen and substantia nigra of MitoPark PD mice. Comparisons were made with behavioral test and histology.

METHODS: Animal models: MitoPark ($DAT^{+/cre}$-$Tfam^{loxP/loxP}$) Parkinson's disease mice (n=6, 3 female and 3 male, 30 weeks old) and age-matched control mice (n=6, C57BL/6J, male) and were imaged under 1.1% isoflurane under spontaneously breathing. Rectal temperature was maintained at 37.0±0.5°C. Respiration rate, heart rate and arterial oxygen saturation were also monitored and maintained within normal physiological ranges.

MRI: MRI scans were performed on a 7T Bruker with a 1cm surface coil. For CBF maps, EPI was used with TE=12 ms; TR=3s; NT=100; 9 slices; THK=1 mm. For ADC and FA maps, 2D diffusion-weighted spin-echo EPI was used: TE=32 ms; TR=3s; NT=8; 11 slices; THK=1 mm; diffusion direction=30, FOV=12.8x12.8mm and matrix=64x64. For $T2^*$ maps, 3D MGE sequence was used: TE=2+2.5n ms (n=0~9); TR=1s; NR=4; FOV=12.8x12.8x8mm; matrix=128x128x80.

Data analysis: Matlab codes were used to calculate the BF, ADC, and T2* maps. ROI values of the substantia ngira (SN) and caudate putamen (CPU) were quantified. Group-average values were tabulated and statistical test employed student t-test (confidential interval 95%, 2 tails) between groups.

Histology: 30 µm thick midbrain sections from 30-week old MitoPark mice and control littlermates were stained with tyrosine hydroxylase.

RESULTS: CBF, ADC and $T2^*$ in CPU and SN of the MitoPark mice were reduced compared to controls, but only $T2^*$ reached significant difference ($p<0.01$) (**Figure 1**). FA was not statistically different between MitoPark and control (data not show).

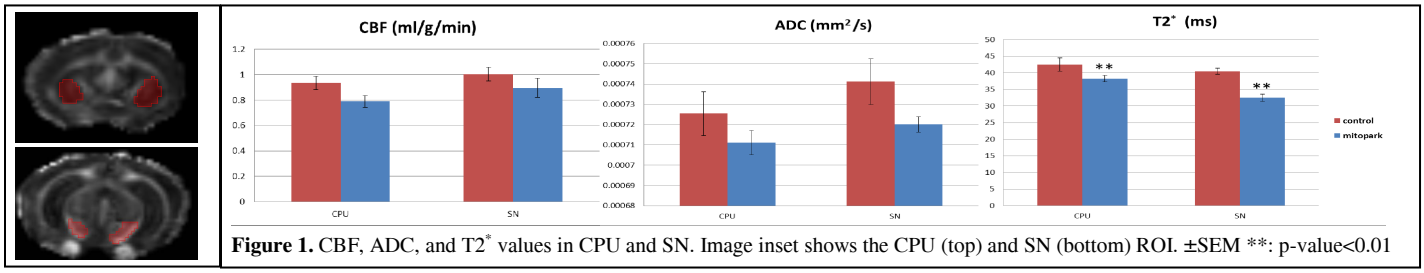

Figure 1. CBF, ADC, and $T2^*$ values in CPU and SN. Image inset shows the CPU (top) and SN (bottom) ROI. ±SEM **: p-value<0.01

Figure 2 shows the apparent loss of tyrosine hydroxylase-positive dopamine neurons in substantia nigra parc compacta (SNpc) in a MitoPark mouse compared to a control. Behavior test showed that MitoPark mice exhibited progressive loss of motor activities, as indicated by significant difference in horizontal ($P<0.001$) and vertical ($P<0.01$) loco-motor activity compared to controls (**Figure 3**).

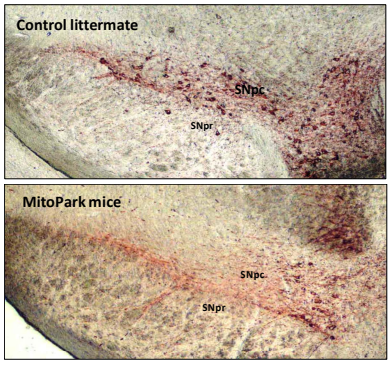

Figure 2: Stain for tyrosine hydroxylase

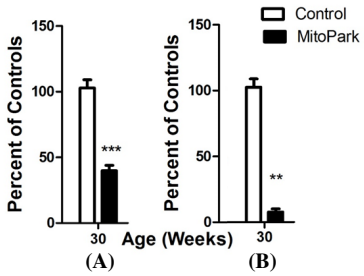

Figure 3: Behavioral data. A is horizontal activity; B is vertical activity.
Error bars: SEM. ***: p<0.001; **: p<0.01

DISCUSSION and CONCLUSION: Reduced $T2^*$ in CPU and SN in MitoPark mice is suggestive of increased iron accumulation in these brain regions. This result is consistent with human PD studies, in which PD patients exhibit higher iron levels in basal ganglia, particularly the SN and caudal putamen, compared with healthy controls [3,4].

MitoPark mice showed trends of lower ADC and CBF in CPU and SN compared to controls (albeit not significantly). Such mild hypoperfusion suggests vascular changes and reduced brain activities, consistent with the reduced motor activities [2]. Mild reduction in ADC suggests structural changes, including loss of cellular density. We anticipate that ADC and CBF changes will become statistically significant with increasing sample sizes.

To our knowledge, this is the first MRI study of a novel, clinically relevant model of PD (MitoPark) that recapitulates some critical clinical features. Future studies will increase sample sizes, incorporate other MRI measurements (such as resting-state fMRI and susceptibility MRI), study earlier time points aimed at early detection, and use MRI to longitudinally evaluate novel neuro-protective therapies.

Reference: 1) Wu, Arch Neurol 2011. 2) Li, PloS one 2013. 3) Wallis, J Magn Reson I 2008. 4) Dexter, J Neurochem 1989.