MPTP Mouse Model of Parkinson's Disease – Imaging Modalities for Metabolic, Anatomical and ^{1}H-Spectroscopic Changes

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1 OVERVIEW

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms, including, rigidity, difficulty of movement, and impaired with walking and gait. The main pathological feature of PD is the cell death of dopaminergic neurons located in the substantia nigra pars compacta (SNc) and substantial loss of dopamine (DA) and its metabolites, and reduced dopamine active transport (DAT) activity. Imaging technologies have been used to monitor the progression of PD as well is supporting criteria for Parkinson's diagnosis. DA plays an important role in the mediation of movement, cognition and emotion. Loss of DA-containing neurons in striatum, results in a loss of DA transporters (DAT) in the presynaptic nerve terminals and hence the reduction of DAT density is inversely correlated with the severity of motor dysfunction. In this work we have used various imaging tools in mouse model of systemic administration of MPTP by using T2-MRI, ^{1}H-MRS and PET imaging (DAT and glucose consumption).

MPTP (20 mg/kg, i.p.) was administered two times a day with 3h-interval on two consecutive days. On week 2 and 5 MPTP treated mice showed small but non-significant trend towards anatomical atrophy in various brain structures. In addition, on same time points MPTP mice showed significant changes in cellular metabolites in striatum when compared to vehicle treated mice. PET imaging of ^{18}F-FE-P2I was performed on week 5, clear and significant decrease in DAT binding saturation point was seen in MPTP mice. Furthermore, and supporting the ^{1}H-MRS findings we observed that glucose consumption by FDG-PET was significantly decreased at week 6 after the MPTP challenge when compared to healthy mice. Taken together, MPTP challenge creates a permanent and long term phenotype which can be evaluated by various imaging techniques, in addition to conventional biochemical and histological and immunohistochemical means.

2 MRI AND MRS

Metabolite analysis from striatum of MPTP (n=12) and vehicle (n=10) treated mice was performed using proton MR Spectroscopy (Figure 1). Further, possible volumetric changes in striatum, cortex and whole brain were evaluated from MRI images (Figure 2). As a summary, in brain metabolites significant ($p<0.05$, unpaired t-test) changes were seen in Ala, Cr, PCr, GLU, INS, Lac, Cho on D12 and in Ala, Glc and Lac on D35. No significant changes ($p<0.05$, unpaired t-test) in brain volumetry between MPTP and vehicle treated mice was observed in either time point.

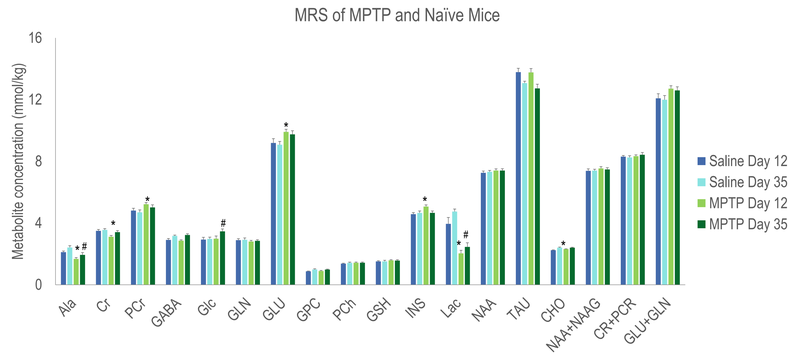


Figure 1. Metabolites from BRAIN REGION of MPTP (n=12) and vehicle (n=10) treated mice. Values shown as mean +SEM. Significant (*$p<0.05$) changes were seen in Ala, Cr, PCr, GLU, INS, Lac, Cho on D12 and in Ala, Glc and Lac on D35 (#$p<0.05$).

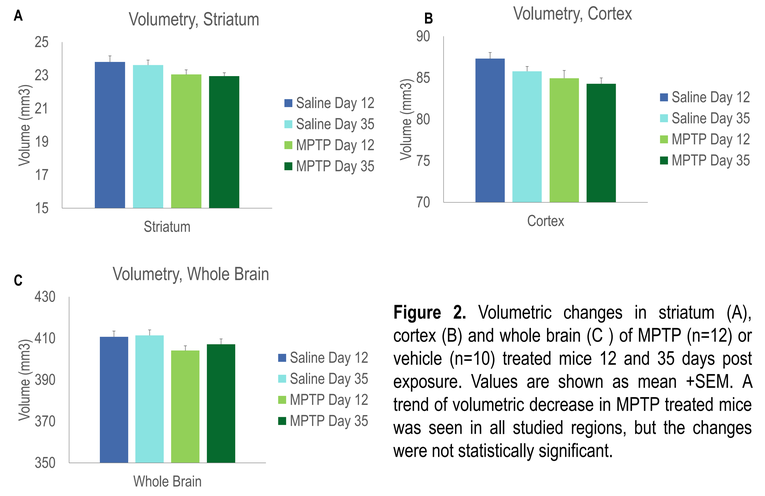


Figure 2. Volumetric changes in striatum (A), cortex (B) and whole brain (C) of MPTP (n=12) or vehicle (n=10) treated mice 12 and 35 days post exposure. Values are shown as mean +SEM. A trend of volumetric decrease in MPTP treated mice was seen in all studied regions, but the changes were not statistically significant.

3 RECEPTOR DENSITY CHANGES

Loss of dopaminergic cells in Parkinson's disease was modelled with MPTP challenge. Dopamine transporter availability and glucose metabolism were studied using ^{18}F-FE-PE2I and ^{18}F-FDG, respectively (Figures 3 and 4). Significant ($p<0.05$, t-test) decreases in the BP_{ND} of DAT ligand and glucose metabolism in MPTP exposed mice were observed suggesting dopaminergic neuronal death characteristic to Parkinson's disease.

After *in vivo* imaging, the brains of the mice were collected and maximal binding (Bmax) of tritiated radioligands to corresponding receptors in cortex, striatum, globus pallidus and substantia nigra was determined using autoradiography.

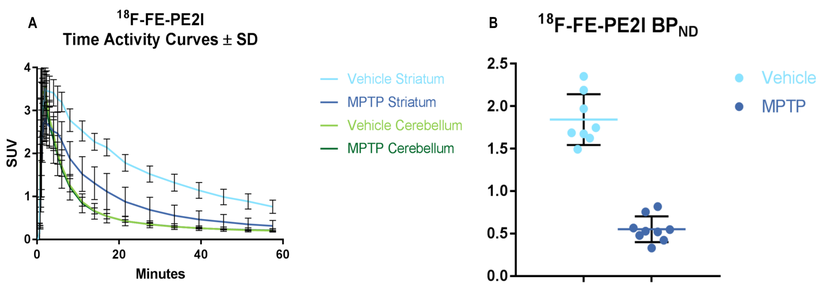
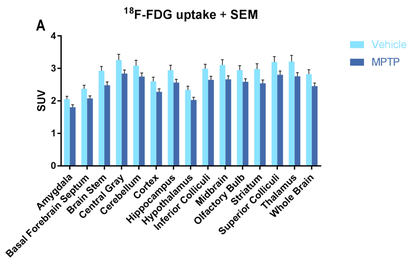


Figure 3. A) Time activity curves from striatum and cerebellum of vehicle (n=8) and MPTP (n=9) treated mice. As no binding of used radioligand, ^{18}F-FE-PE-2I, to cerebellum was seen, it could be used as reference region to model non-displaceable binding potential (BP_{ND}). B) Individual BP_{ND} including mean values and SD were calculated using SRTM. MPTP treated mice showed 70.1% decrease in BP_{ND} when compared to vehicle treated group (unpaired two-tailed T-test, **** $p < 0.0001$).



ROI	P value
Amygdala	0.04
Basal Forebrain Septum	0.04
Brain Stem	0.01
Central Gray	0.06
Cerebellum	0.09
Cortex	0.05
Hippocampus	0.05
Hypothalamus	0.03
Inferior Colliculi	0.07
Midbrain	0.03
Olfactory Bulb	0.04
Striatum	0.03
Superior Colliculi	0.07
Thalamus	0.05
Whole Brain	0.04

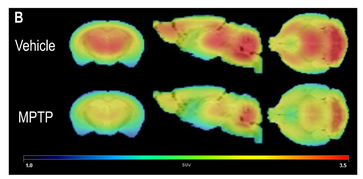
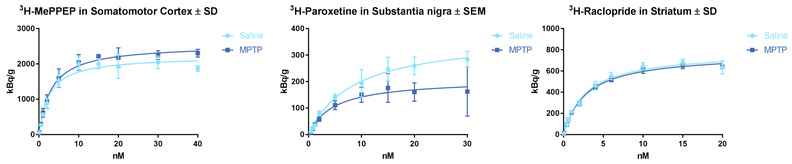


Figure 4. A) SUV values of FDG accumulation to studied brain regions. Values are shown as mean +SD. MPTP treated mice showed significant (unpaired t-test) decrease in majority of of the regions of interest (ROI) when compared to vehicle treated mice. B) Averaged PET images of ^{18}F-FDG 30 – 50 min post injection showed lower uptake in MPTP treated mice (n=9) compared to vehicle treated group (n=8). The PET images were coregistered with mouse MRI template prior PET analysis. Sections shown in coronal, sagittal and horizontal views.



MePPEP (CB1)	Difference	
Globus pallidus	-7.92 %	P = 0.28
Cingulate Cortex	**34.00 %**	**P < 0.0001**
Somatomotor Cortex	**14.68 %**	**P = 0.0005**
Striatum	-1.35 %	P = 0.76

Paroxetine (SERT)	Difference	
Substantia nigra	**-43.95 %**	**P < 0.0001**

Raclopride (D2/3R)	Difference	
Striatum	-2.29 %	P = 0.46

Figure 5. Various receptor densities between MPTP (n=4) and vehicle (n=4) treated mice were studied using Bmax assay of radioligand to its target receptor and autoradiography. As a summary, significant ($p<0.05$) decrease of SERT (SNC), increase of CB1 (Cing & SomCortex) and increase of GABA (CingCortex) in MPTP mice was observed compared to naïve. No difference in D2/3R receptor density between MPTP and naive mice.

4 CONCLUSIONS

In this study we have evaluated translational imaging modalities to study both anatomical and functional differences in MPTP induced model of Parkinson's disease. Further, alterations in receptor densities were analysed post mortem. The results were in line with findings in clinical patients suggesting these methodologies to be relevant readouts in PD drug development programs.