METABOLIC CHANGES DETECTED BY PROTON MAGNETIC RESONANCE SPECTROSCOPY IN VIVO AND IN VITRO IN A MURIN MODEL OF PARKINSON'S DISEASE, THE MPTP-INTOXICATED MOUSE

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Purpose/Introduction:

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of the dopaminergic neurons in the substantia nigra pars compacta (SNc), which project to the striatum. Besides dopamine (DA) depletion in the striatum, reactive increase in glutamatergic drive in the basal ganglia has been suggested to be central to the expression of PD motor symptoms. Changes in glutamatergic systems include overactive corticostriatal transmission [1]. The aim of this study was to analyze *in vivo* and *in vitro* striatal glutamate changes in a mouse model of PD.

Subjects and Methods:

The study is performed on 7 C57Bl6/J control mice and 7 MPTP-intoxicated mice (MPTP, 25mg/kg, administered i.p. once daily during 5 days). *In vivo* MRS acquisitions are performed at 9.4T. Mice are anesthetized and carefully placed on an animal handling system with the head centered in birdcage coil (diameter 20mm) used for both excitation and signal reception. Spectra are acquired in a voxel ($2\times2\times2$ mm) centered in the striatum using PRESS (TE=8.844ms, TR=4s, VAPOR [3] water suppression, spectral width of 5kHz and accumulating 512 scans). After *in vivo* MRS acquisitions, mice are sacrificed; successful lesion is verified by TH immunolabeling on the SNc and *in vitro* MRS acquisitions are performed on perchloric extracts of anterior part (which overlaps the striatum) of mice brains. *In vitro* spectra are acquired on the 9.4T magnet using a high resolution $^{1}H/^{13}C$ probe (diameter 5mm), TR=5s, a spectral width of 2kHz and accumulating 246 scans. NMR spectra were fitted by jMRUI software using the time-domain QUEST algorithm based on a metabolite basis set [4] for *in cand* using AMARES for *in vitro*. Metabolite levels assessed are expressed as a function of internal water content obtained from the unsuppressed water signal for *in vivo* data and as a function of the internal reference TSP (20mM) for *in vitro*. Measurements are compared by analysis of variance (ANOVA), followed by a Dunnett post-hoc test to determine the significance.

Results:

Fig.1 shows a spectrum acquired *in vivo* from the striatum presenting signals of mainly glutamate (Glu), glutamine (Gln), total choline (tCho), total creatine (tCr), NAA, taurine (Tau), myo-inositol (Myo-Ins) and lactate (Lac). No significant difference are observed *in vivo* except for Glu. Its concentration is more important in striatum of MPTP-lesioned mice. The *in vitro* (fig.2) results confirm this increase, Glu (6.39±0.54 vs 7.98±0.23µmol/g, $p<0.05$), GABA (1.19±0.13 vs 2.10±0.23µmol/g, $p<0.01$) and Gln (3.46±0.30 vs 4.57±0.30µmol/g, $p=0.074$) are significantly more important in MPTP-lesioned mice.

Discussion/Conclusion:

The striatal Glu increasing described *in vivo* and confirmed *in vitro* underlines the overactive glutamatergic corticostriatal transmission in the MPTP-lesioned mouse, model of PD. Several assumptions could explain increase of GABA in the striatum, (i) a reinforced GABAergic activity in the striatum, (ii) a glutamate uptake, then metabolized in GABA for detoxification. The increase of Gln could confirm this second hypothesis, in fact Glu and Gln metabolisms are linked and Gln synthesis is a detoxification pathway after Glu exposition.

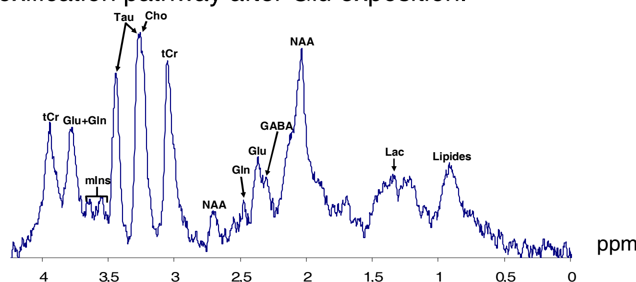

Fig.1. In vivo spectrum acquired from the striatum of a control mouse.

References :

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[2]. Tkac et al. MRM, 1999. **41**(4):p.649-56.

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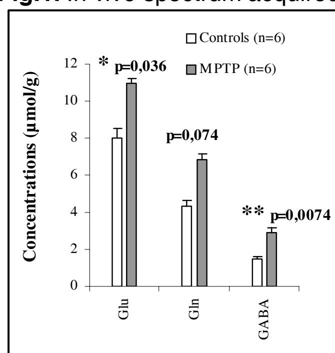

Fig 2. Concentrations of brain metabolites quantified by jMRUI.
In vitro in the anterior part of control and MPTP-lesioned mice.