Neurochemical changes in the early stage of Huntington's disease progression studied in transgenic mice using ^{1}H and ^{31}P NMR spectroscopy

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INTRODUCTION

Wide ranging metabolic changes were previously detected using *in vivo* ^{1}H NMR spectroscopy at middle and end stage disease in the neurochemical profile of the striatum of the most severe model of Huntington's disease, the R6/2 mouse [1]. To address whether metabolic changes occur early in disease progression, ^{1}H NMR spectra were obtained for the young Q111 mouse, a very mild HD model [2].

METHODS

All NMR measurements were performed using a Varian INOVA spectrometer interfaced to a 9.4 T magnet, equipped with powerful 2nd-order shim coils (Magnex). First and second order shims were adjusted by FASTMAP [3]. Ultra-short echo-time STEAM (TE = 2 ms) combined with outer volume suppression and VAPOR water suppression was used for ^{1}H NMR spectroscopy [4]. Metabolite concentrations were quantified using LCModel with macromolecule spectra included in the database and the unsuppressed water signal was used as an internal reference [5]. ^{31}P NMR spectra were acquired using ISIS with broadband adiabatic RF pulses (R = 40 – 80). Metabolites were quantified using line-fitting method and a scaling factor determined from the average signal intensity of PCr in control mouse group and concentration calculated from ^{1}H spectra. Signal intensities were corrected for saturation using measured T_1 relaxation times. CD1 mouse strain was used as a control.

RESULTS AND DISCUSSION

Transgenic Q111 as well as control CD1 mice were measured at 6 and 13 weeks of age using ^{1}H and ^{31}P NMR spectroscopy. ^{1}H spectra were measured from striatum and ^{31}P spectra from dorsal areas covering cortex, hippocampus and dorsal striatum (Fig. 1). Most significant changes were observed for Cr, PCr, Gln, and Tau in striatum of Q111 mice relative to CD1 controls (Fig. 2). Changes in ATP levels were not observed (Fig. 3). Surprisingly, Gln increases were observed despite the very early stage of the disease in this slowly progressive model in agreement with published results from R6/2 HD model [1]. Significant changes in PCr/Cr ratio (p = 0.0001) observed in striatum at 6 weeks became normal at 13 weeks, indicating a compensatory process to maintain the homeostasis.

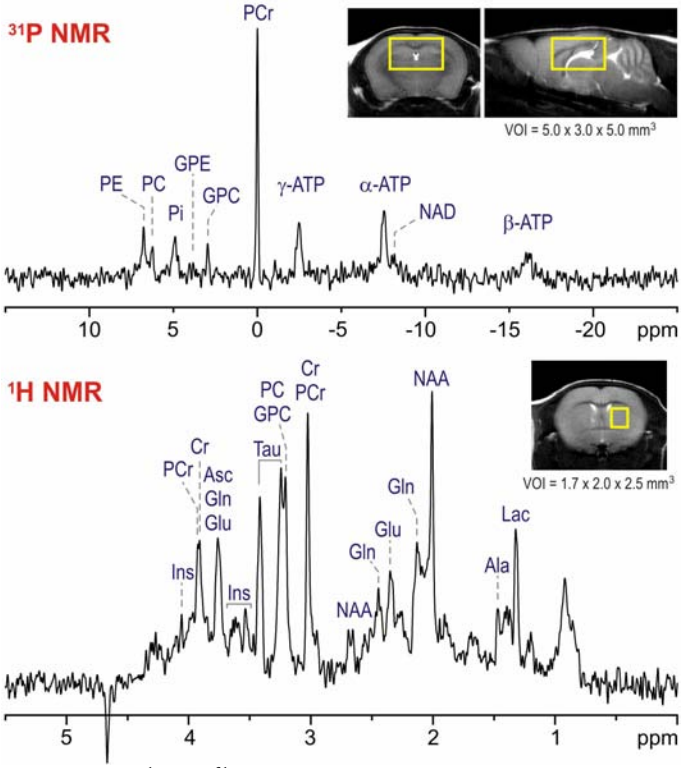

Fig. 1 In vivo ^{1}H and ^{31}P NMR spectra measured from the brain of Q111 Huntington's disease transgenic mouse. ^{1}H NMR: STEAM, TE = 2 ms, TR = 5 s, NT = 240. ^{31}P NMR: ISIS, TR = 5.5 s, NT = 600. Insets: FSE images with the locations of the VOI.

REFERENCES: 1. Tkac I et al., *J Neurochem* 2006 (in press); **2.** Wheeler VC et al., *Human Molecular Genetics* 8: 115-122; **3.** Gruetter R and Tkac I, *Magn Reson Med* 2000: 43, 319-323; **4.** Tkac I et al., *Magn Reson Med* 1999: 41, 649-656; **5.** Pfeuffer J et al., *J Magn Reson* 1999: 141, 104-120.

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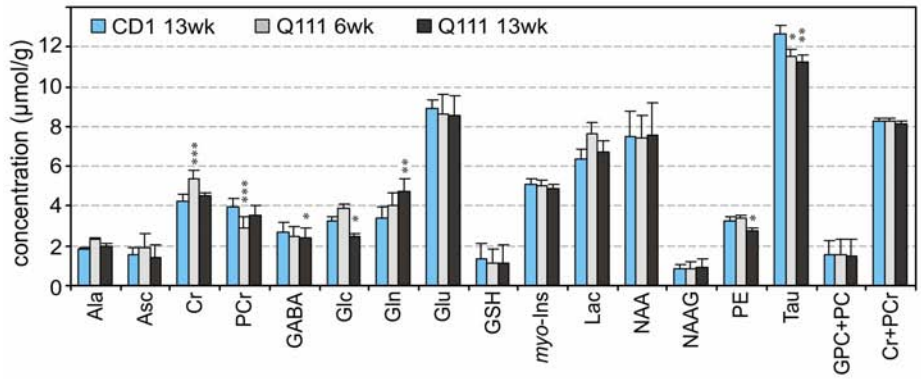

Fig. 2 Early changes in the neurochemical profile in striatum of Huntington's disease transgenic mice (Q111) measured at 6 and 13 week of age relative to the control (CD1). Data quantified from ^{1}H NMR spectra. Mean ± SD, n = 9 in each group, * p < 0.02, ** p < 0.002, *** p < 0.0002

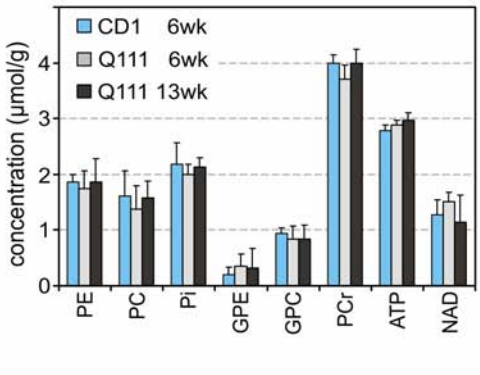

Fig. 3 Metabolites quantified from ^{31}P NMR spectra in Q111 mice and CD1 controls (see Fig. 2). Mean ± SD, n = 4 in each group.