In vivo longitudinal ^{1}H MRS study of transgenic mouse models of prion disease in the hippocampus and cerebellum at 14.1T

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Introduction:

In vivo ^{1}H MRS allows non invasive characterization of brain metabolism and it has been used for studying brain metabolic changes in a wide range of neurodegenerative diseases. The prion diseases form a group of fatal neurodegenerative diseases, also described as transmissible spongiform encephalopathies (TSEs), which are caused by abnormal conformational isomers (PrP^{Sc}) of the host-encoded prion proteins (PrP^{c}) (1). Both, the physiological function of PrP^{c} and the molecular pathways leading to neurodegeneration in prion disease remain unknown. Consequently, different transgenic mouse models of prion disease were created to study the role of the PrP^{c}. These models were crucial in elucidating precursor-product relationship between PrP^{c} and PrP^{Sc}. Among these models, the mice lacking prion protein (Prnp -/-) developed normally and no severe pathologies were observed (2). In contrast, mice expressing PrP which lacks defined domains ($PrP_{\Delta 32\text{-}121}$) suffer from ataxia, astrogliosis and cerebellar granule cell loss (3). These findings accentuate the need for a non-invasive and longitudinal investigation technique which could bring additional information. From our knowledge, no in vivo MRS study was performed in transgenic mouse models of prion disease. Therefore, we performed an in vivo longitudinal ^{1}H MRS study at 14.1T with the aim to measure the neurochemical profile of Prnp -/- and $PrP_{\Delta 32\text{-}121}$ mice in the hippocampus and cerebellum, respectively.

Methods:

Mice lacking prion protein (Prnp -/- mice) and mice expressing PrP which lacks defined domains ($PrP_{\Delta 32\text{-}121}$) were created as described in ref (2) and (3), respectively. ^{1}H spectra were measured at 6 and 12 months of age on 18 mice (6 Prnp-/-, 6 $PrP_{\Delta 32\text{-}121}$ and 6 wild type (WT)). Anesthesia was maintained at 1.3 ± 0.2 % of isoflurane in oxygen, body temperature was kept at 36.5 ± 0.2 °C. All data were acquired on a 14.1T/26cm system (Varian/Magnex Scientific) using a home-built 14mm x 21mm quadrature coil as RF transceiver and an ultra-short-echo time SPECIAL spectroscopy sequence (TE=2.8ms, TR=4s, 400 scans) (4). The static field was shimmed by FASTMAP. A VOI of 1.3×2×2.2mm^3 was selected in the hippocampus and a second VOI of 2x2.5x2mm^3 was selected in the cerebellum. After first and second order shimming, the typical linewidth of water resonance at TE=2.8 ms was 18-23 Hz. Metabolite concentrations were estimated using LCModel (5), combined with a simulated basis-set of metabolites and the spectrum of macromolecules measured in vivo. Absolute metabolite concentrations were obtained using unsuppressed water signal as a reference.

Results and Discussion:

No difference in theT_2 weighted image appearance was observed between the WT and Prnp -/- or $PrP_{\Delta 32\text{-}121}$ animals. In general, spectra exhibited excellent signal-to-noise ratio and notable differences in metabolite signals were discernable (Fig. 1).

The neurochemical profile (mean ± SEM) measured at 12 months in the hippocampus and cerebellum of Prnp -/, WT and $PrP_{\Delta 32\text{-}121}$ mice is shown in Fig. 2. For the Prnp -/- mice at 6 months the overall neurochemical profile was similar to the WT in the hippocampus and cerebellum (data not shown). However, at 12 months a significant increase of Glu (30%), Ins (20%) and Lac (100%) was noticed in the hippocampus. A significant increase of Lac (100%) was also observed in the cerebellum. The $PrP_{\Delta 32\text{-}121}$ mice showed no significant changes in the hippocampus at 6 months; however a significant increase of Ins (15%) and Glu (20%) was found in the cerebellum (data not shown). At 12 months we observed a significant decrease of tNAA (20%) in both hippocampus and cerebellum. The significant increase in Ins noticed in the cerebellum at 6 months was also observed at 12 months (17%).

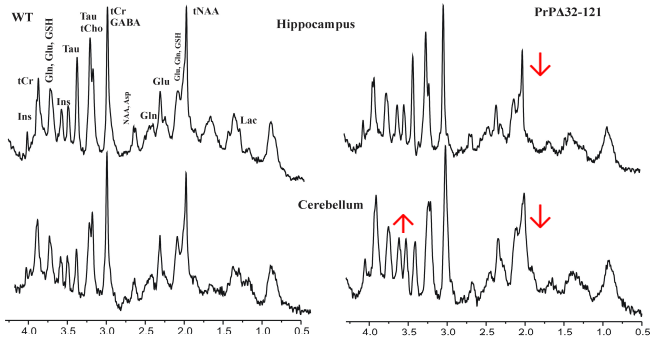

Fig. 1: SPECIAL ^{1}H spectra acquired at 12 months old in the hippocampus and cerebellum of a WT and $PrP_{\Delta 32\text{-}121}$ mouse.

We evaluated for the first time the in vivo concentration of 19 metabolites at 6 and 12 months in the hippocampus and cerebellum of Prnp -/- and $PrP_{\Delta 32\text{-}121}$ mice, respectively. In contrast to histology and behavioral tests (2) where no significant changes were observed, our data showed significant changes in the brain metabolism of Prnp -/- mice. The increase of Glu, Lac and Ins in the hippocampus at 12 months seems to indicate a dysfunction in the neurotransmitter metabolism and astrogliosis.

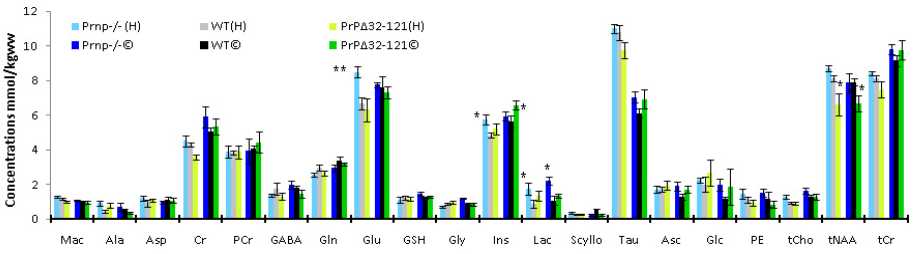

Fig. 2: Neurochemical profile (mean ± SEM) in the hippocampus (H) and cerebellum © of Prnp -/, WT and $PrP_{\Delta 32\text{-}121}$ mice at 12 months old. **<0.005, *<0.03

The decrease of tNAA detected in $PrP_{\Delta 32\text{-}121}$ mice in both hippocampus and cerebellum at 12 months seems to reflect neuronal loss in agreement with the histological findings (3). In addition, the increase of Ins in the cerebellum at 6 and 12 months may reflect astrogliosis related to an inflammatory process, consistent with the histological features (3).

In conclusion, high-field MR spectroscopy is capable of detecting changes in brain metabolism of Prnp-/- and $PrP_{\Delta 32\text{-}121}$ mice compared with the WT animals and consequently provides additional information.

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