CORE
Metadata, citation and similar papers at core.ac.uk
Provided by Infoscience - École polytechnique fédérale de Lausanne

Short-echo-time ^{1}H MRS of the mouse lacking prion protein (Prnp-/-) at 14.1T

C. Cudalbu[1], V. Mlynárik[1], J. Bremer[2], A. Aguzzi[2], and R. Gruetter[1,3]

[1]Laboratory for Functional and Metabolic Imaging (LIFMET), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, [2]Institute of Neuropathology, University Hospital of Zurich, Zurich, Switzerland, [3]Departments of Radiology, Universities of Lausanne and Geneva, Switzerland

Introduction:

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). The mechanism by which prions elicit brain damage and the relative contributions of PrP^{Sc} accumulation and PrP^{c} depletion to the prion replication remains unclear. Consequently, different animal models were created in order to study the role of the PrP^{c}. Among these models, knockout mouse models were crucial in elucidating the precursor-product relationship between PrP^{c} and PrP^{Sc}. On histologic analysis of tissue, spongiform degeneration and astrocytic gliosis was observed in mice lacking of prion protein (2). In vivo ^{1}H MRS allows non invasive characterization of brain metabolism and it has been used to study brain metabolites changes in a wide range of neurodegenerative diseases. Only a very few reports describing the use of in vivo ^{1}H MRS in prion disease have been published so far (3-5), reporting only a few metabolites (mainly NAA). From our knowledge, no in vivo MRS study was performed until now in mice lacking prion protein (Prnp -/-). Therefore the aim of our study was to use in vivo high-resolution ^{1}H MRS at 14.1T to measure the neurochemical profile in Prnp -/- mice.

Methods:

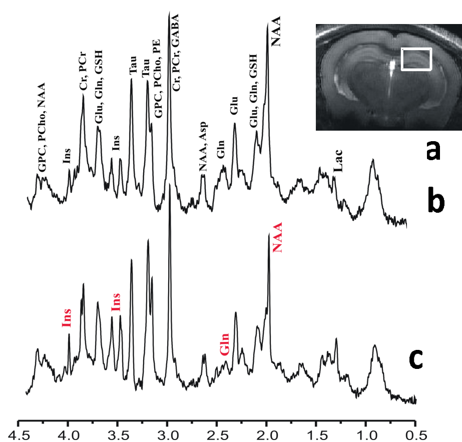
Mice lacking prion protein (Prnp -/- mice) were created as described in ref (6).^{1}H spectra were measured on 11 mice (4 Prnp -/- (16months old), 4 Prnp -/- (8 months old) and 3 wild type (16 months old)). Anesthesia was maintained at 1.3 ± 0.2 % of isoflurane in oxygen, body temperature was kept at 36.5 ± 0.2 °C. All data were acquired on a 14.1T/26cm system (Varian/Magnex Scientific) using: a home-built 14 mmx21 mm quadrature coil as RF transceiver and the ultra-short-echo time SPECIAL spectroscopy sequence (TE=2.8ms, TR=4s, 400 scans) (7) shimmed using FASTMAP. A VOI having the size of 1.3mm×2mm ×2.2mm was selected in the hippocampus. 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 (8), combined with a simulated basis-set of metabolites and the spectrum of macromolecules measured in vivo. Absolute metabolite concentrations were obtained using the unsuppressed water signal as a reference.

Results and Discussion:

Fig. 1a presents coronal views of a Prnp-/- mouse brain indicating the VOI. No differences in signal intensity on theT_2 weighted images were observed between the wild type and Prnp -/- animals. In general, spectra exhibited excellent signal-to-noise ratio (Fig. 1b and c) and notable differences in metabolite signals between the wild type and Prnp -/- mice were discernable (Fig. 1c), such as Ins, Gln, NAA. In the knockout mice the overall neurochemical profile was similar to the wild-type, with the exception of Ins which was significantly increased (~30% with p=0.03) (Fig. 2). In addition Glu, Gln, NAA showed a trend of decrease (~15-30%) in the Prnp -/- mice (Fig. 2). Between the two Prnp -/- groups consistent increase in Ins and decrease of Gln, Glu and NAA were observed. Even if Gln showed an interesting trend of decrease, visually observed also in the spectra, it remains to be solidified with increasing the number of wild type animals.

In contrast to all previous studies performed on humans or mice models injected with CJD or scrapie agent (ME7 strain) (4-5), we have evaluated for the first time the in vivo concentration of 18 metabolites in the hippocampus of Prnp -/- mice. The increase of Ins and the trend towards a decrease in Gln detected may reflect gliosis, consistent with the histological features reported by ref (2) in mice lacking of prion protein, whereas the reduced NAA, Gln and Glu seem to indicate a dysfunction in the neurotransmitter metabolism.

In conclusion, high-field MR spectroscopy is capable of detecting changes in brain metabolism of Prnp-/- mice compared with the wild type animals and consequently provides additional information.



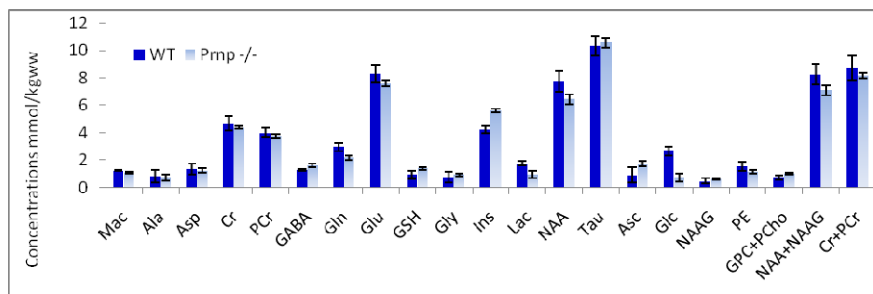


Fig. 2: Neurochemical profile (mean ± SEM) in the hippocampus of wild type and Prnp -/ mice.

Fig 1: a) A coronal views of a Prnp-/- mouse brain indicating the VOI; b) and c)SPECIAL ^{1}H spectra (TE=2.8 ms, VOI = 5.7 µl, 400 scans) acquired in the hippocampus of a wild type and a Prnp -/- mouse, respectively.

References [1] Prusiner SB, Science 1991;252:1515, [2] Nazor KE et al., Biochim Biophys Acta 2007;1771:645, [3] Cordery RJ et al., Eur Radiol 2006;16:1692, [4] Broom KA et al., Neurobiology of Disease 2007;20:707, [5] Behar K et al., Magn Reson Imaging 1998;16:963, [6] Büeler et al., Nature 1992;356:577, [7] Mlynarik V et al., J Magn Reson 2008;194:163, [8] Provencher SW, Magn Reson Med 1993;30:672.

Acknowledgements. Supported by Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL, the Leenaards and Jeantet Foundations, and by the EU Grant No. MRTN-CT-2006-035801.