In vivo MRI of axonal damage with subtle myelin defects in PLP-null mice

S. Boretius[1], S. Goebbels[2], A. Burzynska[1], R. Tammer[1], K-A. Nave[2], J. Frahm[1], and T. Michaelis[1]

[1]Biomedizinische NMR Forschungs GmbH, Max-Planck-Institut fuer biophysikalische Chemie, Goettingen, Germany, [2]Neurogenetik, Max-Planck-Institut fuer experimentelle Medizin, Goettingen, Germany

Introduction

Proteolipid protein (PLP) constitutes half of the myelin protein in the CNS. Mice in which the PLP gene is inactivated develop axonal swelling and degeneration with rather normal-appearing myelin sheaths. At the ultrastructural level, however, PLP-null mice show subtle myelin defects including incomplete compaction [1] and defects in the intraperiod line [2]. The purpose of this study was to investigate how T1- and T2-weighted 3D MRI as well as magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI) reflect axonal damage and subtle myelin disturbances. The results were compared with other animal models exhibiting different degrees of demyelination and/or axonal involvement [3, 4].

Methods

Five PLP-null mutants and 5 controls at the age of 14 months underwent in vivo T1-weighted (3D FLASH, TR/TE = 17/7.58 ms, $\alpha = 25°$) and T2-weighted MRI (3D FSE, TR/TE = 3000/98.25 ms, 16 echoes, inter-echo-spacing = 12.5 ms) at 2.35 T (Bruker Biospin GmbH, Germany). Maps of MTR were based on spin density-weighted FLASH with (Msat) and without (M0) off-resonance irradiation [5]. MTR was given in percent and calculated as (M0–Msat)/M0. All measurements were obtained with an isotropic resolution of 117 µm.

A second group of 10 PLP-null animals at the same age (5 mutants, 5 controls) underwent DTI (half Fourier DW single-shot STEAM, b=10/1000 s mm^{-2}, 125×125×500 µm^3 resolution) at 9.4 T (Bruker Biospin GmbH, Germany) to obtain maps of fractional anisotropy (FA) as well as radial and axial diffusivity. After MRI animals were sacrificed and prepared for histology.

Results and discussion

Compared to controls, PLP-null mutants showed clear alterations of white matter contrast on both T1- and T2-weighted images. White matter structures such as corpus callosum, capsule interna, and ventral hippocampal commissure appeared with signal reductions on T1-weighted and signal increases on T2-weighted images (**Fig.1**, arrows). In contrast, Cnp1-null mutants characterized by axonal degeneration but normal myelination showed similar alterations in T2 but unchanged T1 contrast (**Fig. 2**). A third model of cuprizone-treated mice with acute demyelination but only marginal axonal damage presented with a contrast inversion of white matter on both T1- and T2-weighted images (**Fig.2**). Taken together, these findings demonstrate that T2 contrast is highly sensitive to both myelin disturbances and axonal damage; whereas T1 changes are more likely to reflect myelin distortions.

In PLP-null mutants MTR, FA, and axial diffusivity of the corpus callosum were significantly decreased, whereas the radial diffusivity remained normal (**Fig.3**). Because MTR and radial diffusivity are commonly altered with myelin disturbances, the observed pattern may indicate a different responsiveness and/or reflect additional tissue properties. The observed reduction of the axial diffusivity can be explained by axonal damage.

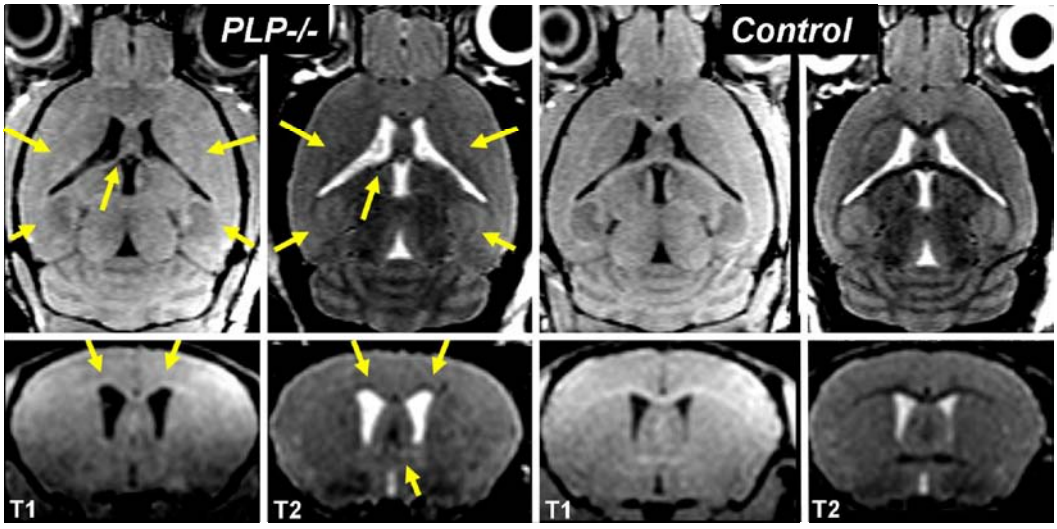
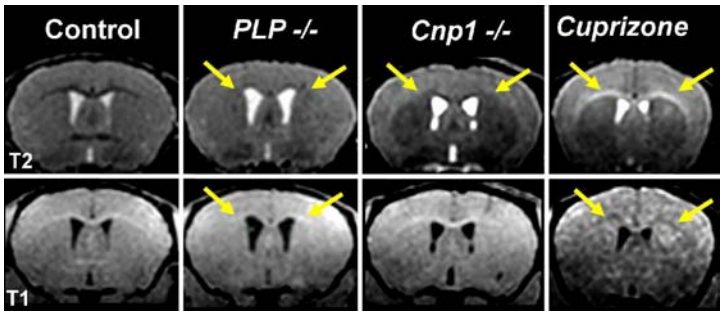


Fig. 1: T1- and T2-weighted MR images of a PLP-null mouse and a control. Arrows indicate a reduction of T1 and T2 contrast in several white matter structures.



Conclusion

The PLP-null mutant is a useful complementary model to study neurodegeneration by MRI. Axonal damage with subtle myelin disturbances yielded a decreased T1 and T2 contrast, a reduction in MTR, as well as a decrease of FA and axial diffusivity. The observed contrast alterations in PLP-null mutants are clearly different from MRI changes detected in Cnp1-null mutants and cuprizone-treated mice. Without doubt, rodent models with well-defined neuropathologic changes can contribute to clarify the molecular and cellular basis of MRI signal abnormalities in human white matter.

Fig. 2: T1- and T2-weighted MR images of a control, PLP-null mutant, Cnp1-null mutant (12 month old), and cuprizone-treated mouse. Arrows indicate the different T1 and T2 contrast alterations in the corpus callosum.

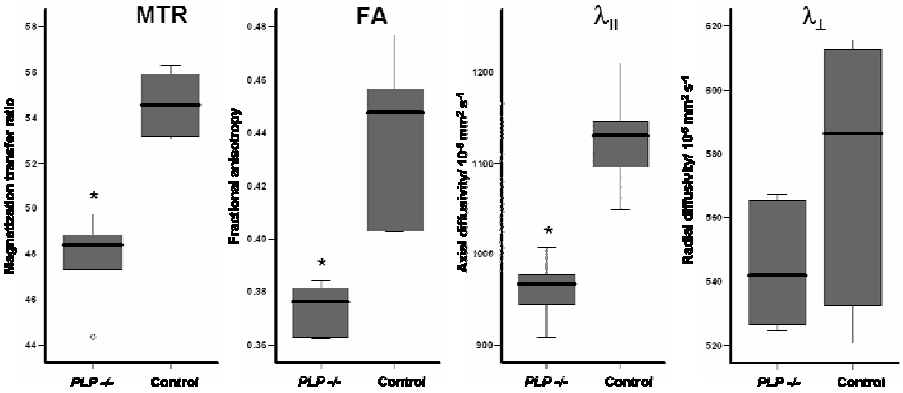


Fig.3: Box plots of magnetization transfer ratio, fractional anisotropy, axial and radial diffusivity of PLP-null mice and controls (p<0.05, Mann-Whitney-U test)*

References

1. Rosenbulth et al., Glia 54:172-182, 2006
2. Yool et al., Neuropathol Appl Neurobiol 28:75-78, 2002
3. Boretius et al., ISMRM 16:25, 2006
4. Merkler et al., NMR Biomed 18:395-403, 2006
5. Natt et al., Magn Reson Imaging 21:1113-20, 2003