Viscoelastic properties change at an early stage of Cuprizone induced affection of Oligodendrocytes in the Corpus Callosum of C57/black6 mice

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Introduction

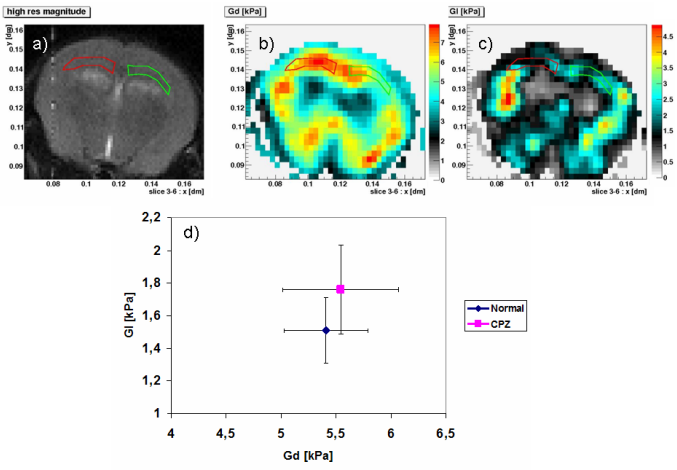
Magnetic resonance elastography (MRE) is an innovative imaging technique developed to non-invasively map and quantify the viscoelastic properties of tissue *in vivo*. MRE has been used as a tool to image and assess human tissue properties in several areas of the body such as breast tissue, prostate and skeletal muscle and brain[1,2]. As pathological alterations cause changes in elasticity and viscosity, MRE might well be applied to characterize the structural integrity of a given tissue and could be employed for diagnosis and clinical monitoring of neurodegenerative diseases such as multiple sclerosis. Therefore it appears to be essential to evaluate the effect of pathological processes occurring in multiple sclerosis, as there are neuronal and axonal degeneration, demyelination and incomplete remyelination, on the viscoelastic properties of cerebral tissue with the help of experimental rodent models. Thus, we introduced the cuprizone (CPZ) mouse-model which depicts key features of multiple sclerosis, namely demyelination and reactive gliosis.[3,4] The feeding of the neurotoxicant CPZ to a group of C57/black6 mice induces transient demyelination of the murine central nervous system, mimicking the myelin damage and loss caused by neuroinflammation.

Methods

A total amount of 60 mice has been included in this study. In our experiment, the CPZ-added diet will be delivered for a period of 6 weeks, followed by 6 weeks of regular feeding. According to our hypothesis, the first phase of our study will reveal early occult alterations of the biomechanical properties caused by demyelination, and in the second phase we expect a remyelination ad integrum. At this stage, 6 healthy mice and 6 CPZ-fed mice after 3 weeks of treatment have been compared. Longitudinal mechanical waves at 1000Hz were transmitted into the mouse brain. The animal was anesthetised using Isoflurane and body temperature was kept constant during the entire examination (1.5h). Full 3D MRE was performed with a total of 10 slices and an isotropic image resolution of 300µm. In addition, high-resolution T2-weighted anatomical scans were acquired with identical slice positioning. Reconstructed maps of the complex-valued shear modulus $G^* = Gd + iGl$ were thresholded in order to segment the area of the corpus callosum (cc). A Landau-fit to the remaining distribution provided mean-peak-values (MPV) and variances for Gd and Gl.

Results

High resolution mouse brain images were obtained using a T2-weight sequence (RARE) (Fig 1a). The obtained maps for the elasticity (Fig.1b) and viscosity (Fig.1c) show very high correlation to the expected anatomy showing the CC and other structures like the basal ganglia as rather stiff and viscous regions. The comparison of Gd and Gl in the CC after 3 weeks of CPZ-treatment shows a slight but statistically significant **INCREASE** in the viscoelastic properties for the CPZ-mice.



Discussion

High-resolution MRE at 7T in mouse brain has been demonstrated and the maps of the viscoelastic properties agree very well with the expected anatomical features. In particular, we observe a very high spatial correspondence between the CC as seen on the high-resolution RARE images and the Gd/Gl-maps. Interestingly, the CPZ-mice exhibit an increase in viscoelastic properties compared to the control group. In principle, a demyelination should lead to a reduction of tissue integrity and hence to a drop in mechanical properties. However, the CPZ-model induces shortly after its onset a multitude of pathological effects, e.g. an increase in the number of cells in the CC (astrocytes, microglia/macrophages) and morphological changes in astrocytes such as hypertrophy and process-thickening.[4] These effects could lead to the observed stiffening of the tissue within the CC. The subsequent histological analysis as well as the continuation of this longitudinal study should provide an answer to this effect.

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