# MR Properties of Neural Tissue Following Experimentally Induced Demyelination

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**Introduction**

The process of demyelination is often associated with a number of neural pathologies including multiple sclerosis and trauma. Distinguishing the pure demyelination processes from inflammation or tissue degeneration like axonal loss is challenging because of similar qualitative changes in the MR signal intensities in the $T_1$, $T_2$ or Magnetization Transfer (MT) weighted images. The purpose of this study was to measure how the process of demyelination alone affects quantitative MR measurements. To achieve this goal, we have used an experimental animal model of neural tissue demyelination [1] by applying tellurium (Te) diet in weanling rats. The weanling rats fed a Te diet exhibit paralysis of the hind limbs, an effect, which is attributed to segmental demyelination of the axons in the sciatic nerves.

**Experimental Methods**

We measured MR properties of rat sciatic nerve *in vitro* after one to seven days of applying 1.1% by weight of Te diet in 9 weanling rats per each day. As controls, 5 untreated nerve samples per day were also measured. For quantitative evaluation of neural tissue integrity, a computer-assisted image analysis (CAIA) was performed on the toluidine blue-stained samples using image analysis software (Image-Pro Plus 4.5, Media Cybernetics, Silver Spring, MD). The myelin content and extracellular matrix volume (EM) fraction were calculated as percentages of total sampled area. All MR measurements were performed at 20°C and 1.5 T on a 20 cm bore superconducting magnet (Nalorac Cryogenics Corp, Martinez, CA) controlled by a SMIS spectroscopy console (SMIS, Surrey, England). The MR measurements consisted of the following:

- $T_1$ relaxation (35 TI values logarithmically spaced from 1 to 32,000 ms);
- multicomponent $T_2$ relaxation (CPMG, TE/TR=1/10,000 ms, 2000 even echoes sampled and 100 averages)
- quantitative Magnetization transfer (MT) was measured using a continuous wave (cw) saturation pulse of 7 s duration. For the standard MTR evaluation, the RF saturation pulse amplitude, $\omega_1/2\pi$ was 670 Hz and the offset frequency of the saturation, $\Delta$ was 5 kHz. To quantitatively evaluate MT data [2] four RF saturation amplitudes ($\omega_1/2\pi$ = 85, 170, 670 and 2670 Hz) and 26 off-resonance frequencies $\Delta$ (ranging from 0.014 to 250 kHz) were applied. The repetition time TR was 10 s, the number of averages was four.

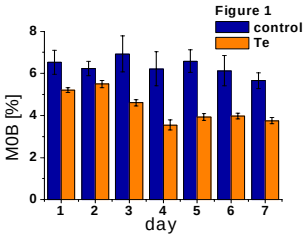
$T_1$ data were analyzed assuming mono-exponential behaviour. All $T_2$ decay data were fitted to a multicomponent $T_2$ model in which the relaxation of each $T_2$ component has a Gaussian distribution on a logarithmic time scale [2]. Moreover, the single measure of the $T_2$ relaxation, $\langle T_2 \rangle$ was evaluated. $\langle T_2 \rangle$ represents an average of the $T_2$ relaxation spectrum and is equivalent to the mono-exponential estimate of $T_2$ decay that is usually assessed in clinical MR. Quantitative MT data were fitted to a "two-pool" model [3] quantifying the exchange between an unrestricted liquid pool and a semisolid macromolecular pool of restricted mobility. The model estimates: R, the rate of exchange of longitudinal magnetization between liquid and semisolid pools as well as $M_{0B}$, the fraction of magnetization that resides in semisolid pool and undergoes MT exchange, $R_A$, the intrinsic longitudinal relaxation rate constant in liquid pool and $T2_B$ – transverse relaxation rate constant of the semisolid pool.

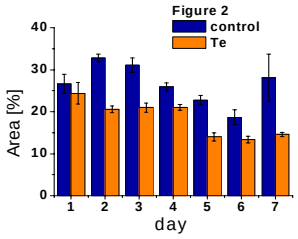
**Results**

Te diet significantly decreased myelin content over time and did not appear to injure axons directly or cause inflammation. Most of the measured MR parameters changed with demyelination: Table 1. shows the MR parameters between control sample and sample with Te diet after 4 days.

| | Myelin [%] | $T_1$ [ms] | $\langle T_2 \rangle$ [ms] | Area of Short $T_2$[%] | Intermediate T2 [ms] | $M_{0B}$ [%] | $1/R_A$ [ms] | R [$s^{-1}$] | MTR [%] | $T2_B$ (μs) |
|---|---|---|---|---|---|---|---|---|---|---|
| Control | 33±2 | 706±68 | 67±8 | 26±2 | 76±10 | 6±2 | 695±70 | 50±3 | 49±1 | 8.5±0.1 |
| Te diet | 23±3 | 912±18 | 106±8 | 21±2 | 107±10 | 3.6±0.8 | 909±19 | 57±5 | 48±2 | 8.4±0.1 |

The average relaxation times, $\langle T_1 \rangle$ and $\langle T_2 \rangle$ and the value of the intermediate $T_2$ component increased with decrease of myelin content, whereas the MT semisolid fraction $M_{0B}$, MTR and the area of short $T_2$ decreased during demyelination process. The MT exchange rate R was constant and independent of demyelination. As an example, Fig. 1,2 show the average $M_{0B}$ and area of short $T_2$ for samples with Te diet and control as a function of time (days).




**Discussion**

Tellurium diet provided an excellent model of demyelination with minimal damage to axons alone and lack of inflammation. The quantitative comparison between measured MR parameters and histopathology showed that the 32% change in myelin content induced significant change in most MR parameters and allowed us to used them as a quantitative evaluation of the degree of demyelination. For example, by day four, the $\langle T_1 \rangle$ and $\langle T_2 \rangle$ relaxation times increased approximately 38 and 58% (respectively), whereas MTR decrease was smaller (approximately 1%). The changes in more quantitative MR measures, such as the value of intermediate $T_2$ component (approximately 41% increase) and MT macromolecular fraction $M_{0B}$ (approximately 43% decrease) were also pronounced. Other MR parameters, such as relative curve areas of the short $T_2$ component spectra, which is thought as the best indicator of myelin change [2] decreased also significantly with demyelination (approximately 20% ) and the results were even more pronounced for day seventh (approximately 48%). This is in contrast to the processes of inflammation [5] where the change in the short T2 component area is not significant. Interestingly, the MT exchange rate, R seems to be independent of demyelination. The moderate change in MTR (up to 10% for day 7) due to demyelination may be explained by conflicting contributions of the MT and direct effects to the MTR [4]. In the case of demyelinated nerves, the decrease in MTR caused by decreased $M_{0B}$ is possibly counteracted by the decreased longitudinal relaxation rate, $R_A$. The multi-component T2 relaxation seems to be the best technique in distinguishing between the processes of myelin loss and inflammation.

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