Changes of Proton T_1 and T_2 Relaxation Times of Cerebral Metabolites Induced by Repeated Manganese Treatments in Rat

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Introduction Chronic overexposure to manganese leads to selective deposition of the metal in the globus pallidus (GP) and clinical symptoms that resemble those found in Parkinson's disease[1]. Recently in vivo ^{1}H MRS was applied to study the effects of Mn neurotoxicity on cerebral metabolism in human and non-human primate[2-3] exposed to manganese chronically. The results showed that, compared to control, the patients had mildly reduced N-acetylaspartate (NAA)/creatine (Cr) ratio in the basal ganglia[2], and the manganese-treated non-human primates had significantly decreased NAA/Cr ratio in the frontal white matter[3]. Yet Mn^{2+} is a paramagnetic ion that can enter neurons via voltage-gated Ca^{2+} channels, and it may affect the T_1 and T_2 relaxation times of both intracellular and extracellular metabolites, thus affecting their quantification. In fact, it has been demonstrated in phantom experiments that the presence of Mn^{2+} reduces the T_1 of NAA and Cr methyl resonance[4]. In this study, Mn^{2+}-induced changes in the T_1 and T_2 of water, NAA and Cr were measured in vivo at 4.7 T in the GP of rats subjected to repeated manganese exposures.

Materials and Methods Male SD rats (180-250 g) received daily i.p. injection of $MnCl_2$ (120 mmol/L, 3 ml/kg) for five consecutive days. T_1-weighted imaging and in vivo ^{1}H MRS were performed on isoflurane (1.5-2.0%, in 70:30 N_2O /O_2) anesthetized rats before injection, on 2d before the 2nd injection and 1d after the last injection (i.e., on 6d) on a 4.7T/30cm Bruker Biospec scanner. A 12-cm diameter Helmholtz volume coil was used for excitation and a 2.5-cm diameter surface coil for reception. A PRESS sequence was used to acquire ^{1}H spectra from the GP with a voxel size of 2.5 mm×2.5 mm×2.5 mm (Fig. 1). Spectral data obtained in saturation-recovery (SR) experiments were used to calculate T_1 of metabolites, and the changes of metabolite peak intensities with total TE was used to calculate T_2. the T_1 of water and metabolites was measured with TE 136 ms and 9 TR values ranging from 0.5 to 10 s, and the T_2 with TR=2 s and 6 TE values ranging from 30 to 272 ms. Statistical analysis was performed with one-way ANOVA followed by post hoc Tukey's test.

Results A ^{1}H spectrum acquired from the GP of a Mn^{2+}-treated rat is shown in Fig. 1. Compared to control, the T_1 and T_2 of NAA and Cr methyl resonance at 2.02 ppm and 3.0 ppm had insignificant decreases after the 1st treatment, while the T_1 and T_2 of water reduced significantly by about 26±5% and 6±1%, respectively. After 5 Mn^{2+}-treatments, the T_1 of NAA, Cr and water reduced significantly by 14±16%, 35±24% and 41±7%, and the T_2 by 26±15%, 12±10% and 12±1%, respectively.

Discussion The T_1 and T_2 of water decreased significantly already after the first treatment and further reduced after 5 treatments, suggesting that the concentration of Mn^{2+} in the GP increased as the rats had more Mn^{2+} treatments, agreeing with the results of Hazell et al[5]. It was estimated that at the injection dose used in this study, the Mn^{2+} concentrations in the GP were about 1.6 μg/g and 7.3 μg/g, respectively, after one and five treatments. The T_1 and T_2 of NAA and Cr had a trend to decrease after the first treatment and such reductions became statistically significant after 5 treatments, suggesting that the T_1 and T_2 of metabolite also depend on the Mn^{2+} concentration in the brain region where they are measured. Therefore, when in vivo ^{1}H MRS is used to assess Mn^{2+}-induced cerebral metabolic changes, the effects of relaxation time changes induced by the presence of Mn^{2+} should be taken into account in metabolite quantification, and this can be done by optimizing the spectroscopic acquisition parameters[4]. For example, using the T_1 and T_2 relaxation data obtained in this study and assuming the concentrations of metabolites do not changes, relaxation-induced signal intensity changes for NAA and Cr methyl resonance after 5 Mn^{2+} treatments would be 1.1% and 0.9%, respectively, if TR of 6 s and TE of 20 ms are used, and the changes will increase to 4.4% and 11.7%, respectively, if TR of 1 s and TE of 136 ms are used.

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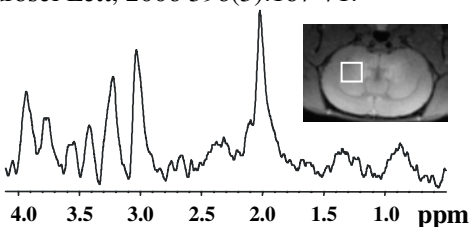

Figure 1: T_1-weighted image and localized ^{1}H spectra (TR/TE: 6000/20 ms) acquired from the globus pallidus of a rat treated with $MnCl_2$ for 5 days.

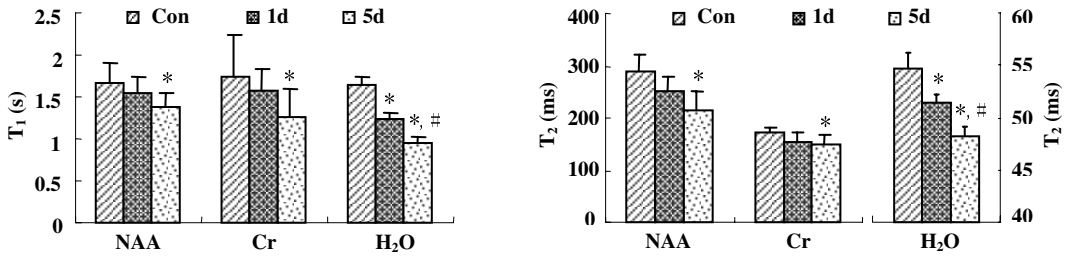

Figure 2: T_1 (A) and T_2 (B) relaxation times of water and metabolites in the globus pallidus of control rats (con) and rats treated with $MnCl_2$ for 1 day (1d) and 5 days (5d). *p<0.05, compared to control, # p<0.05, compared to 1d.