A model of competition between Manganese and Iron and their combined influence on R1 in Rat Brain Tissues

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Background: Mn and Fe are both strongly paramagnetic ions [1,2] that may to some degree share a common transport system into tissues. It is well known that in simple solutions a linear relationship exists between the concentration of paramagnetic ion and the relaxation rate: $R_{1,2}([Ion]) = R_{1,2}(0) + k_{1,2}[Ion]$, where $k_{1,2}$ are the relaxivities [1]. We have previously shown that the relaxivities of manganese vary in different brain regions [3]. The situation becomes more complicated when both manganese and iron concentrations vary in tissues.

Methods: Rats were randomly separated as: control (CN), treated (MnT), Fe deficient but Mn treated (FeDMnT), Fe supplemented but Mn treated FeSMnT groups. MnT, FeDMnT, FeSMnT groups are given weekly intravenous injection of isotonic Mn^{2+} solution equivalent to 3 mg Mn/kg body weight for a total of 14 weeks. CN and MnT are given normal diet food, FeDMnT and FeSMnT groups are given Fe deficient food and Fe supplemented food respectively. All rats were scanned every other week. T1 and T2 values were measured from regions of interest (ROIs) in rat brain images acquired using a 4.7 T Varian imaging system. At the end of the study, brains were removed and dissected. Mn concentrations in brain samples were measured with graphite furnace AAS.

Results: Mn concentrations were not significantly different between FeDMnT and FeSMnT groups. Significant increases of Mn accumulation are observed in the FeDMnT and FeSMnT groups compared to CN in cerebellum (p =0.0002), brainstem (p=0.0003), striatum (p=0.001), and cortex (p<1e-5), and these regions except cerebellum also have significantly higher Mn concentration compared to MnT group. Mn content of the FeDMnT and FeSMnT groups is significantly decreased in hippocampus compared to CN (p<0.1) and MnT (p<1e-5). Iron level (not shown here) decreased significantly in cerebellum (p<1e-6), brainstem (p<0.001), midbrain (p=0.003) and cortex (p=1e-4) compared to CN and MnT. A simple linear fit was first applied according to the following equation: $R_1([Mn],[Fe]) = R_0 + k_{1,Mn} * [Mn] + k_{1,Fe} * [Fe]$. However, the resulting $k_{1,Fe}$ is negative for most of the brain regions (results not shown here) which has no clear physical interpretation. The failure of the linear model and the results of AAS both suggest that manganese and iron interact competitively and their combined influence on relaxation rates is complicated.

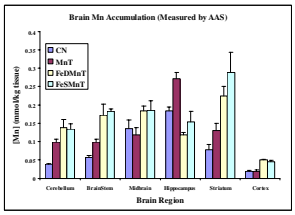

Fig 1. Brain Manganese Accumulation

Table 1. Results of fitting model

	Cerebellum	Brainstem	Midbrain	Hippocampus	Striatum	Cortex
BS_{total}	0.139	0.328	1.222	0.256	1.970	0.035
$K_{eq,Mn}$	334.220	18.402	33.235	3972.600	53.656	1024.633
$K_{eq,Fe}$	124.250	383.382	402.094	5.383	103.246	96.897
$k_{1,MnB}$	2.616	7.811	2.145	0.000	1.547	6.893
$k_{2,MnB}$	23.199	64.240	16.917	4.051	9.633	45.873
$k_2/k_{1,MnB}$	8.867	8.224	7.888	N/A	6.227	6.655
$k_{1,FeB}$	0.003	0.000	0.147	1.646	0.000	0.707
$k_{2,FeB}$	0.239	0.071	4.677	0.995	0.000	0.000
$k_2/k_{1,FeB}$	88.787	N/A	31.876	0.604	0.000	0.000

Model: We propose a new model to consider the competition between manganese, iron and their influence on relaxation rates. In this model, iron and manganese compete for a common binding site. In any specific brain region, both manganese and iron can be separated into two pools—either bound to a common binding site (MnB, FeB) or unbound (MnO, FeO) which includes free ions or metal bound to other substrates. Five equations (Eqs.1 to 5) are used to describe the model, where $K_{eq,Mn}$ and $K_{eq,Fe}$ are the equilibrium constants, BS_{free} and BS_{total} are the free binding sites and total binding sites in a brain region, Mn_{total} and Fe_{total} are the total Mn and Fe metals measured by AAS. The longitudinal relaxation rate R1 is influenced by the combined effects of MnB, FeB, MnO, FeO as described by Eq. 6. The parameters in Eqs. 1-6 can be estimated in a least-squares sense by the following steps. First, a set of initial values of the eight unknown parameter are given. Then the nonlinear equations are solved by the Levenberg-Marquardt method [4] using the initial values of parameters and the values of measured manganese and iron concentrations. Next, R0 and relaxivities are fit using measured R1 data according to Eq. (6). The algorithm is a subspace trust region method and is based on the interior-reflective Newton method described in [5]. Once the convergence criteria are met and the eight parameters are updated, the above procedure is repeated until a local minimum of residual error is found. To search for the global minimum, a Monte Carlo simulation scheme is used to set initial values randomly and the final regression results are compared with the experimental R1 measurements. The solution with the largest correlation coefficient is used in this study. The transverse relaxivities were also calculated. Some results are shown in Table 1.

$$K_{eq,Mn} = \frac{[MnB]}{[MnO] * [BS_{free}]} \quad (1)$$

$$K_{eq,Fe} = \frac{[FeB]}{[FeO] * [BS_{free}]} \quad (2)$$

$$[BS_{total}] = [MnB] + [FeB] + [BS_{free}] \quad (3)$$

$$[Mn_{total}] = [MnB] + [MnO] \quad (4)$$

$$[Fe_{total}] = [FeB] + [FeO] \quad (5)$$

$$R_1([Mn]) = R0 + k_{1,MnB} * [MnB] + k_{1,MnO} * [MnO] + k_{1,FeB} * [FeB] + k_{1,FeO} * [FeO] \quad (6)$$

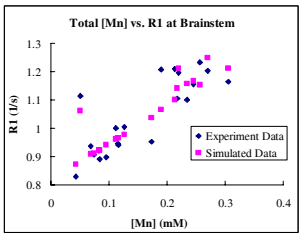

Fig. 2. Total [Mn] vs. R1 at

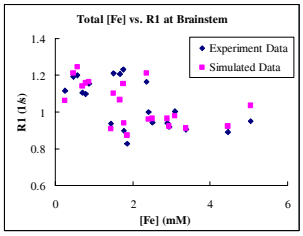

Fig. 3. Total [Fe] vs. R1 at

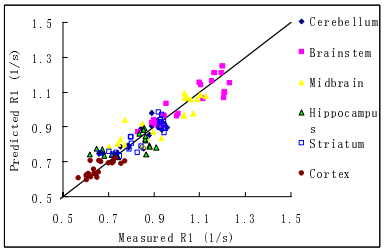

Fig. 4. Comparison between measured and predicted R1

Discussion: In this model, the concentrations of total binding sites in midbrain and striatum are apparently much higher than the other regions. The common binding sites in hippocampus and cortex have higher affinity for manganese as $K_{eq,Mn}$ is much larger than $K_{eq,Fe}$, while the ones in brainstem and midbrain are more likely to bind with iron. The increase in relaxation rates is mainly due to the manganese and iron that are bound as the relaxivites of FeO and MnO are very small (results not shown here). In most of the brain regions, manganese that is bound shows a larger relaxation effect than the bound Fe, but in most areas the relaxivity is less than for free metal ion. However, in hippocampus, the relaxivities for manganese and iron groups (either bounded or others) are both small, suggesting that in this brain region, the competing manganese and iron may both exist in non-paramagnetic states. Figs. 2, 3, and 4 show that the nonlinear relationships between R1 and [Mn] as well as R1 with [Fe] are well explained by this model. This model may be useful for interpreting MR results when more than one paramagnetic species is involved.

References:

1. Kang YS, Gore JC. Invest Radiol 1984;19: 399-407.
2. Gore JC, Kennan RP. Magnetic Resonance Imaging of the Brain and Spine. 1996
3. Zhang N., Fitsanakis V.A., Aschner M., Avison M.J., Gore J.C. ISMRM 2006.
4. Marquardt, D., SIAM Journal Applied Mathematics, 1963; 11: 431-441.
5. Coleman, T.F. and Y. Li, SIAM Journal on Optimization 1996; 6: 418-445.