Quantification of the regional non-hemin iron in human brain in vivo through the apparent transverse relaxation rate of the tissue water at 4.7T

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Introduction

Iron is the most abundant heavy metal in human body. It is an essential element, but the overabundance causes harmful effects through the production of reactive oxygen species. Aceruloplasminemia, neuroferritinopathy, and Friedreich's ataxia are known to be neurodegenerative diseases caused by defects in normal iron metabolism [1]. Recently it has been reported that the occurrence of Alzheimer's and Parkinson's diseases are closely related to the presence of regional iron [2]. Thus, estimation of the brain iron concentration in vivo is relevant to assess the risk of these diseases. We have reported that the apparent transverse relaxation rate ($1/T_2^\dagger = R_2^\dagger$) of the tissue water in human brain at 4.7T has a high linear correlation (R = 0.97) with the published levels of non-hemin iron ([Fe]) [3,4]. This high correlation motivated us to attempt to quantify brain regional [Fe] from the observed $R_2^\dagger$. In the present study we will present two kinds of estimations of [Fe] on 54 healthy subjects (1) by using a simple linear relationship between $R_2^\dagger$ and [Fe], and (2) by considering the regional macromolecular fraction (f_M = 1 – water fraction [5]) as a transverse relaxation source in addition to [Fe].

Materials and Methods

Human brain $T_2^\dagger$ measurements were conducted on 54 (26 male and 28 female) healthy volunteers using a multiecho adiabatic spin echo (MASE) sequence at 4.7T as has previously been described [3]. All the measurements were performed on a 4.7T wholebody MRI system using a TEM head coil. Six echoes were collected with TR/TE of 4000/26-156ms on a transaxial 2.5 mm slice across the basal ganglia. On the T_2 map generated from six echoes $T_2^\dagger$ values were extracted at five GM regions of frontal cortex, caudate, putamen, thalamus, and globus pallidus, as well as at frontal WM. The regional [Fe] was calculated from the obtained $R_2^\dagger$ values in two ways. The first estimation was performed using a linear relationship of $R_2^\dagger = 0.551[Fe] + 14.1$ (equation 1) obtained from separate twelve subjects [3], where $R_2^\dagger$ is in s^{-1} and [Fe] is in mg/100g fresh weight. The second estimation was performed using an equation of $R_2^\dagger = \alpha[Fe] + \beta[f_M] + \gamma$ (equation 2). The parameters of α, β, and γ were obtained by a least square fitting of 6 average $R_2^\dagger$ values measured at previously-mentioned 5 GM and 1 WM regions in 38 subjects over 30 years old with the published [Fe] and f_M values in each region [6,7]. As a result α, β, and γ were given as 0.470, 24.9, and 9.54, respectively.

Results and Discussion

Figure 1 shows [Fe] estimated by the first method at frontal cortex, caudate, globus pallidus, and thalamus in 54 subjects as a function of the age. The age dependent change is obvious. As was described by Hallgren and Sourander, the change at first three GM regions is well fitted with exponential curves (Fig.1a). An exceptional age-dependent decrease at thalamus region was also reproduced (Fig.1b). The average [Fe] estimated at each region in subjects over 30 years old was within ±20% of those reported previously except for thalamus (+43%). The limitations with this simple estimation were (1) the [Fe] value at thalamus was overestimated, (2) [Fe] in WM could not be estimated because the $R_2^\dagger$ in frontal WM did not conform to the regression line between $R_2^\dagger$ in GM and [Fe].

Figure 2 shows the result of fitting of the observed $R_2^\dagger$ at six brain regions with equation 2, which take into account the contribution of relaxation due to f_M in addition to [Fe]. Correlation coefficient between $R_2^\dagger$ and [Fe] increased to 0.99 after considering the contribution from f_M to $R_2^\dagger$. Using equation 2 the regional [Fe] was recalculated. The average [Fe] value recalculated at thalamus in 38 subjects over 30 years was 4.9±2.0 mg/100g fr. wt. vs. the reported value of 4.76±1.16. [Fe] in frontal WM was inclusively estimated to be 4.0±1.7 mg/100g fr. wt. vs. the reported value of 4.24±0.88.

Conclusions

$R_2^\dagger$ obtained in human brain at 4.7T gives good estimates of [Fe] in the brain in vivo. The estimate is significantly improved when the contribution of macromolecular fraction to $R_2^\dagger$ is taken into account.

References

[1] Madsen E, Gitlin JD, Annu. Rev. Neurosci. 30: 317 (2007), [2] Smith DG et al, Biochim. Biophys. Acta. 1768: 1976 (2007), [3] Mitsumori F et al, MRM 58: 1054 (2007), [4] Hallgren B, Sourander P, J. Neurochem. 3: 41 (1958), [5] Rooney WD et al, MRM 57: 308 (2007), [6] Randall LO, J. Biol. Chem. 124, 481 (1938), [7] Gelman N, et al, MRM 45, 71 (2001).

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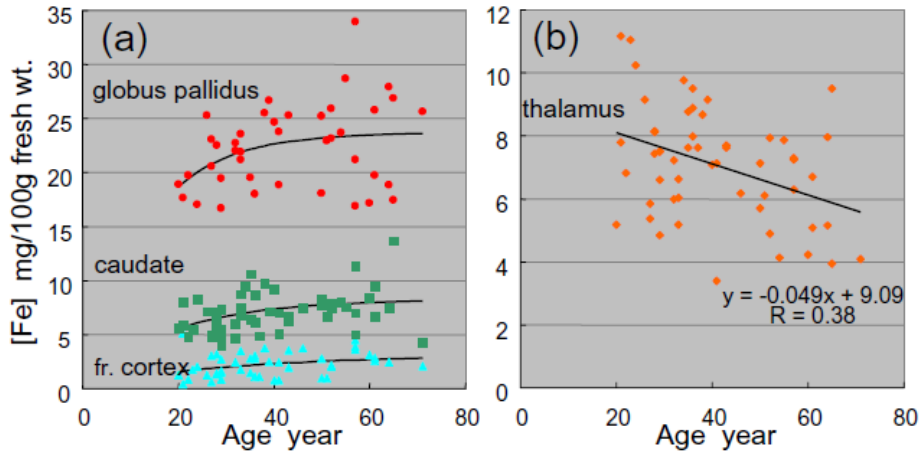

Fig.1. Age-dependent changes in the regional [Fe] estimated from $R_2^\dagger$ using equation 1. Solid lines show exponential regressions in (a), and a linear regression in (b).

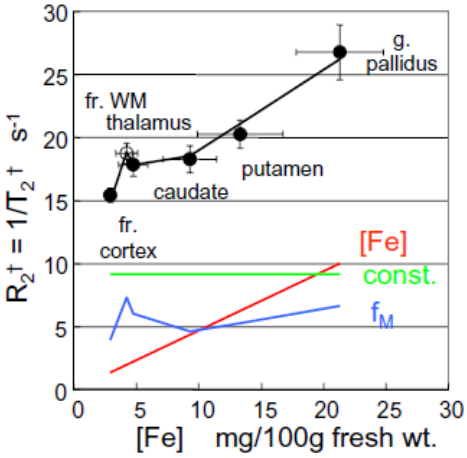

Fig.2. Correlation between the average $R_2^\dagger$ and [Fe] considering the contribution from f_M.