NeuroImage 147 (2017) 488–499

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Changes in brain iron concentration after exposure to high-altitude hypoxia measured by quantitative susceptibility mapping

Lin Chen[a], Congbo Cai[b], Tianhe Yang[c], Jianzhong Lin[c], Shuhui Cai[a,*], Jiaxing Zhang[d,*], Zhong Chen[a]

[a] Department of Electronic Science, Fujian Provincial Key Laboratory of Plasma and Magnetic Resonance, Xiamen University, Xiamen 361005, China
[b] Department of Communication Engineering, Xiamen University, Xiamen 361005, China
[c] Magnetic Resonance Center, Zhongshan Hospital, Medical College of Xiamen University, Xiamen 361004, China
[d] Department of Physiology and Neurobiology, Medical College of Xiamen University, Xiamen 361102, China

ARTICLE INFO

Keywords:
High-altitude exposure
Brain iron
Quantitative susceptibility mapping
Hemisphere difference
Gender difference
Diffusion tensor imaging

ABSTRACT

Hypoxia can induce physiological changes. This study aims to explore effects of high-altitude (HA) hypoxia on cerebral iron concentration. Twenty-nine healthy sea-level participants were tested shortly before and after approximately 4-week adaptation to the HA environment at fQinghai-Tibet Plateau (4200 m), and were re-investigated after re-adaptation to the sea-level environment one year later. Iron concentration was quantified with quantitative susceptibility mapping (QSM), and the results were compared with transverse relaxation rate (R_2^*) measurements. The variations of magnetic susceptibility indicate that the iron concentration in gray matter regions, especially in basal ganglia, including caudate nucleus, putamen, globus pallidus and substantia nigra, increases significantly after HA exposure. This increase appears consistent with the conclusion from R^*_2 value variations. However, unlike QSM, the R^*_2 value fails to demonstrate the statistical difference of iron content in red nucleus. The re-investigation results show that most variations are recovered after sea-level re-adaptation for one year. Additionally, hemisphere- and gender-related differences in iron concentration changes were analyzed among cerebral regions. The results show greater possibilities in the right hemisphere and females. Further studies based on diffusion tensor imaging (DTI) suggest that the fractional anisotropy increases and the mean diffusivity decreases after HA exposure in six deep gray matter nuclei, with linear dependence on iron concentration only in putamen. In conclusion, the magnetic susceptibility value can serve as a quantitative marker of brain iron, and variations of regional susceptibility reported herein indicate that HA hypoxia can result in significant iron deposition in most deep gray matter regions. Additionally, the linear dependence of DTI metrics on iron concentration in putamen indicates a potential relationship between ferritin and water diffusion.

1. Introduction

Iron plays important roles in physiological functions and development of human brain, including oxygen transportation, DNA synthesis and repair, transport of electrons, neurotransmitters metabolism, and production of myelin lipids (Beard and Connor, 2003; Moos and Morgan, 2004; Zecca et al., 2004). However, accumulation and reactivity of iron occur in a series of neurodegenerative diseases (van Bergen et al., 2016; Zecca et al., 2004). Aberrant deposition of iron is increasingly recognized as an important initiator of cell death and is often associated with toxic free radical and pathological damages (Dixon and Stockwell, 2014; Emerit et al., 2001). In addition, high iron levels in some brain regions can predispose individuals to high risk of motor and cognitive function decline (Li et al., 2015; Sullivan et al., 2009). Although pathologic mechanisms of iron deposition have been actively investigated, possible environmental factors, which may influence brain iron concentration, have rarely been mentioned.

High-altitude cerebral edema (HACE) constitutes a life-threatening form of acute high-altitude illness that often occurs in individuals who are rapidly exposed to high altitude (HA) without acclimatization (Kallenberg et al., 2008). Recent studies (Kallenberg et al., 2008; Schommer et al., 2013) demonstrate that HACE is associated with disruption of the blood-brain barrier (BBB) and with iron deposition in the form of hemosiderin (qualitatively characterized by susceptibility weighted imaging technique) in the brain. Moreover, the extent of microhemorrhages in HACE is correlated with the severity of hemosi-

* Corresponding authors.
E-mail addresses: shcai@xmu.edu.cn (S. Cai), zhangjiaxing@xmu.edu.cn (J. Zhang).

http://dx.doi.org/10.1016/j.neuroimage.2016.12.033
Received 9 August 2016; Accepted 13 December 2016
Available online 14 December 2016
1053-8119/

derin deposition. The deposition will remain detectable over several years because hemosiderin cannot be removed after recovery from HACE. However, to the best of our knowledge, reports regarding whether prolonged acclimatization to HA will cause iron deposition in the brain are lacking. While adaptive events occur in human brains in response to hypoxia after acclimatization, such as normal cerebral blood flow and metabolism (Møller et al., 2002), some factors may lead to iron deposition. Minor increment in the permeability of BBB independent of acute mountain sickness (AMS) (see review by Bailey et al., 2009) and the decrease of serum ferritin (Robach et al., 2004) may cause more Fe^{2+} (derived from hemoglobin degradation) to cross the BBB, to be incorporated into ferritin, and to be acquired by cerebral tissues (Beard, 2001; Moos and Morgan, 2004). Therefore, we hypothesize that iron deposition may also occur in cerebral tissues in spite of successful acclimatization to HA. To test this hypothesis, we utilize quantitative susceptibility mapping (QSM), namely a novel MRI technique that can overcome the nonlocal effect of the magnetic field and provide a contrast mechanism for tissues in vivo (Li et al., 2011; Shmueli et al., 2009; Yao et al., 2009), to quantify iron concentration.

In this study, magnetic susceptibility changes of 29 sea-level participants between before and after their expedition to HA environment have been examined. Arterial oxygen saturation (SaO_2) is defined as the content of oxyhemoglobin (diamagnetic) divided by the sum of oxyhemoglobin and deoxyhemoglobin (paramagnetic) in the arterial blood. Hypoxia can cause a decrease in SaO_2 (Rostrup et al., 2005), and thus may lead to an increase of magnetic susceptibility (Wang and Liu, 2015). Therefore, we took variations of the SaO_2 value into account to evaluate the influence of paramagnetic deoxyhemoglobin on susceptibility changes. It has been reported that iron concentration in brain nuclei grows as an exponential function of age (Li et al., 2014). To estimate the influence of time (about one month on HA) on susceptibility values after HA exposure, 15 participants were re-investigated one year later for comparison. Early work has revealed that brain iron levels vary in hemispheres and genders in deep GM regions (Gong et al., 2015; Persson et al., 2015). Additionally, gender differences in AMS have been found in some studies (McDevitt et al., 2014; Vann et al., 2005). Since hemisphere- and gender-related differences on iron concentration and altitude sickness have been reported, we also investigated hemisphere- and gender-related differences in magnetic susceptibility measurements. Moreover, on the basis of current knowledge that (a) hypoxia can cause extensive alteration in brain water mobility, and (b) cerebral iron deposition may influence water diffusion especially in deep GM regions (Lawley et al., 2013; Xu et al., 2015; Zhang et al., 2013), we hypothesized that water mobility might change together with the brain iron levels after HA exposure. Therefore, we utilized diffusion tensor imaging (DTI) to obtain the information regarding the diffusion of water molecules in vivo (Le Bihan et al., 2001), and two DTI-derived metrics, i.e. fractional anisotropy (FA) and mean diffusivity (MD), were measured. Finally, relationships between the brain iron concentration and DTI metrics in six deep gray matter (GM) nuclei among different stages were examined with partial correlation coefficients.

2. Methods

2.1. Participants

Written informed consent from every volunteer was obtained following a complete description of the study. The experimental protocol was approved by the Research Ethics Review Board of Xiamen University. All experiments were carried out according to the approved guidelines.

Participants (n=29) were recruited from the Volunteer-Teaching Team of Xiamen University. They ranged in age from 19 to 21 years old (mean: 20 ± 0.8) and comprised 16 males and 13 females. All volunteers were right-handed, non-smokers. The Body Mass Index (BMI) and questionnaire of each participant indicated that they had normal weight and no history of head injuries or neurological diseases. All MRI scans were completed at sea level and participants were reimbursed for their time.

Participants were investigated before and immediately after they returned from an expedition to Qinghai-Tibet Plateau (4200 m) where they stayed for about four weeks. First, they spent 3 days reaching the sea level of 3650 m where they stayed 4 h. Subsequently, they spent 25 days at 4200 m. Finally, they decreased to 3650 m and then to the sea level during a period of 4 days. During the HA period, the participants did not take any special food and drink that might influence iron intake, and they did not take any medicine to avoid altitude sickness. Fifteen (8 males, 7 females) participants were re-investigated after an interval of one year since they came back to the sea level.

2.2. MRI protocol

All participants were imaged on a 3T Siemens Tim Trio MRI scanner (Siemens, Erlangen, Germany) at the MRI center in Xiamen. A three-dimensional (3D) multi-echo gradient-recalled echo (GRE) sequence was utilized for QSM. The experimental parameters were set as: repetition time (TR)=53 ms, flip angle=15°, slice thickness=2 mm, acquisition matrix size=256×256, field of view (FOV) =240 mm×240 mm, echo time of first echo (TE_1)=3.6 ms, echo spacing (ΔTE)=5.9 ms, number of echoes=8, and bandwidth=240 Hz/pixel. The readout model was monopolar. Both magnitude and phase images were saved for QSM reconstruction.

To convert images from individual participant space into Montreal Neurological Institute (MNI) space, we employed a 3D MPRAGE sequence to obtain T_1-weighted images for the participants. The images were acquired with following parameters: TR=1900 ms, TE=2.7 ms, inversion time (TI)=900 ms, matrix size=512×512×176, FOV=250 mm×250 mm, slice thickness=1 mm, bandwidth=150 Hz/pixel, and flip angle=9°.

A single-shot diffusion-weighted echo planar imaging (EPI) sequence was applied for DTI acquisition. The scan parameters were: TR=6400 ms, TE=95 ms, FOV=220 mm×220 mm, matrix=128×128, slice thickness=3 mm, number of excitation (NEX)=1, and flip angle=90°. Apart from the one without diffusion weighting (b=0 s/mm^2), diffusion weighted images were sequentially acquired in 30 non-collinear directions with the b value of 1000 s/mm^2.

2.3. QSM reconstruction

QSM images were reconstructed using complex k-space data which were separated into magnitude and phase images. On magnitude images, the brain tissue extraction was performed with the brain extraction tool (BET) in FMRIB Software Library (FSL, University of Oxford) (Smith, 2002). To estimate the field map, we performed one-dimensional temporal phase unwrapping in every voxel, and solved nonlinear least squares fitting in an iterative manner (Liu et al., 2013). Subsequently, the region growing algorithm for phase unwrapping was applied to solve the frequency aliasing on the field map (Cusack and Papadakis, 2002). To separate the field generated by local magnetic sources from the background field, we removed the latter by the projection onto dipole fields (PDF) method (Liu et al., 2011).

The inversion of the susceptibility (χ) was ill-conditioned in the Fourier domain, therefore, the morphology enabled dipole inversion (MEDI) algorithm (Liu et al., 2012, 2013) was introduced in this study to solve the problem. The inversion algorithm aimed to solve the following optimization:

$$\chi^* = \mathrm{argmin}_\chi \|M\nabla\chi\|_1 + \lambda\|W(e^{iBL} - e^{iF_D\chi})\|_2^2. \quad (1)$$

The regularization parameter λ was set to 800 according to the discrepancy principle (Morozov, 1966); the mask M was computed