NeuroImage 156 (2017) 232–239

Contents lists available at ScienceDirect

NeuroImage

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

The multi-level impact of chronic intermittent hypoxia on central auditory processing

Eddie Wong[a,b,c,1], Bin Yang[a,d,1], Lida Du[e,f], Wai Hong Ho[a], Condon Lau[a,*], Ya Ke[e,f], Ying Shing Chan[g], Wing Ho Yung[e,f], Ed X. Wu[b,c]

[a] Department of Physics and Materials Science, The City University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China
[b] Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China
[c] Department of Electrical and Electronic Engineering, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China
[d] Department of Radiology, Children's Hospital of Fudan University, Shanghai, People's Republic of China
[e] School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China
[f] Gerald Choa Neuroscience Centre, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China
[g] School of Biomedical Sciences, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

ARTICLE INFO

Keywords:
Functional magnetic resonance imaging
Auditory system
Chronic intermittent hypoxia
Sleep apnea
Rat

ABSTRACT

During hypoxia, the tissues do not obtain adequate oxygen. Chronic hypoxia can lead to many health problems. A relatively common cause of chronic hypoxia is sleep apnea. Sleep apnea is a sleep breathing disorder that affects 3–7% of the population. During sleep, the patient's breathing starts and stops. This can lead to hypertension, attention deficits, and hearing disorders. In this study, we apply an established chronic intermittent hypoxemia (CIH) model of sleep apnea to study its impact on auditory processing. Adult rats were reared for seven days during sleeping hours in a gas chamber with oxygen level cycled between 10% and 21% (normal atmosphere) every 90 s. During awake hours, the subjects were housed in standard conditions with normal atmosphere. CIH treatment significantly reduces arterial oxygen partial pressure and oxygen saturation during sleeping hours (relative to controls). After treatment, subjects underwent functional magnetic resonance imaging (fMRI) with broadband sound stimulation. Responses are observed in major auditory centers in all subjects, including the auditory cortex (AC) and auditory midbrain. fMRI signals from the AC are statistically significantly increased after CIH by 0.13% in the contralateral hemisphere and 0.10% in the ipsilateral hemisphere. In contrast, signals from the lateral lemniscus of the midbrain are significantly reduced by 0.39%. Signals from the neighboring inferior colliculus of the midbrain are relatively unaffected. Chronic hypoxia affects multiple levels of the auditory system and these changes are likely related to hearing disorders associated with sleep apnea.

Introduction

Oxygen is an essential component of life and the brain requires an adequate oxygen supply to function properly. Hypoxia occurs when the oxygen supply to tissues is insufficient and it may lead to brain damage and central nervous system disorders. Chronic hypoxia can occur in a number of health conditions and occupations. These include sleep breathing disorders and working or living at high altitude. Obstructive sleep apnea (OSA) is a relatively common sleeping breathing disorder that affects 3–7% of the population with higher incidence rates in certain subgroups (Punjabi, 2008). Subjects with OSA often have neurocognitive impairments such as difficulties with reasoning, attention, vigilance, learning, and memory (Lal et al., 2012). Chronic mountain sickness (CMS) is a clinical syndrome that affects people who spend long times, either for work or residence, at high altitudes (> 2500 m) (Leon-Velarde et al., 2005). CMS potentially affects many people as more than 140 million work/reside at high altitudes worldwide (Penaloza and Arias-Stella, 2007).

Despite the significant impact of hypoxia on cognitive function, to date, relatively few studies have investigated the impact of hypoxia on central auditory processing, which is critical for effective hearing. Subjects with chronic hypoxia or hypoxemia (low blood oxygen level) conditions have shown reduced auditory performance (Chen, 2002; Sheu et al., 2012), which indicates conditions such as central auditory processing disorder (CAPD), tinnitus, and hearing loss. OSA can

* Corresponding author.
E-mail address: condon.lau@cityu.edu.hk (C. Lau).
[1] Authors contributed equally to this work.

http://dx.doi.org/10.1016/j.neuroimage.2017.05.036
Received 30 December 2016; Accepted 16 May 2017
Available online 19 May 2017

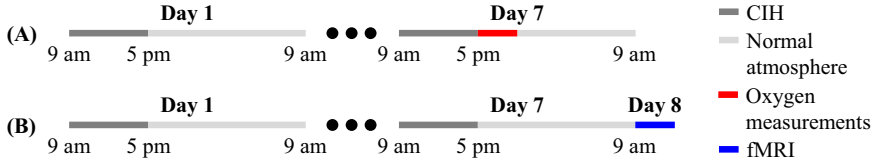

Fig. 1. Rat subjects underwent chronic intermittent hypoxemia (CIH) treatment from 9 am to 5 pm daily for 7 days. During this time, CIH subjects were housed in a gas chamber and the oxygen fraction of the air was varied between 10% and 21% with 90 s period. Note that rats are nocturnal. Subjects were housed in standard cages with normal 21% oxygen air from 5 pm to 9 am. Control subjects also spent 7 days in the same conditions except the oxygen fraction was always 21%. (A) At 5 pm on the 7th day, five subjects from each group underwent blood sampling to measure arterial oxygen partial pressure and oxygen saturation. (B) On the 8th day, eight subjects from each group underwent functional magnetic resonance imaging (fMRI) with broadband sound stimulation.

elevate the minimum detectible sound intensity (Casale et al., 2012), ie. hearing threshold. However, the threshold increase is small and it is important to understand how chronic hypoxia affects central processing. OSA also lowers pitch pattern sequence scores, a measure of central auditory function, even after adjusting for age, gender, obesity, and other variables (Hwang et al., 2011). OSA subjects perform worse in the dichotic digit test, which is an auditory processing assessment (Ziliotto et al., 2006). Furthermore, OSA leads to abnormal auditory evoked potentials, which indicate dysfunction in the central auditory system (Neau et al., 1996; Rumbach et al., 1991; Vakulin et al., 2012; Walsleben et al., 1989). CMS is also often associated with tinnitus, a brain-related hearing disorder where subjects hear phantom sounds (Leon-Velarde et al., 2005).

At present, studies have linked chronic hypoxia conditions with hearing disorders. However, relatively little is understood about the central auditory mechanisms affected by hypoxia. Functional magnetic resonance imaging (fMRI) is well suited to advancing this important research area. fMRI is noninvasive and offers whole brain field of view with relatively high spatial and temporal resolution. fMRI is typically performed with the intrinsic blood oxygenation-level dependent (BOLD) contrast (Ogawa et al., 1990). The BOLD contrast is a MRI measure of the hemodynamic response that follows neuronal activity. fMRI has been applied to study OSA (Archbold et al., 2009; Henderson et al., 2003; Kheirandish-Gozal et al., 2014; Li et al., 2015, 2016; Macey et al., 2006; Park et al., 2016; Zimmerman and Aloia, 2006) and people living/working at high altitude (X.A. Yan et al., 2011; X.D. Yan et al., 2011a, 2011b).

fMRI has also been applied to study central auditory processing in humans (Maeder et al., 2001; Patterson et al., 2002) and animals (Bach et al., 2013; Baumann et al., 2011; Brown et al., 2013). The central auditory system consists of multiple centers, including the cochlear nucleus, superior olivary complex, lateral lemniscus, and inferior colliculus of the brainstem (Musiek and Baran, 2007). Higher up, the medial geniculate body of the thalamus and the auditory cortex are also important auditory centers. Our group has pioneered novel fMRI techniques for investigating the rat central auditory system (Cheung et al., 2012a, 2012b; Gao et al., 2015a, 2014, 2015b; Lau et al., 2015a, 2013, 2015b; Zhang et al., 2013). The rat auditory system is similar to that in humans (Malmierca, 2003). However, subcortical centers such as those in the brainstem and thalamus, are larger in rats relative to the brain size and are more superficially located. This facilitates fMRI studies.

In this study, we examine a chronic intermittent hypoxemia model of OSA (Xie et al., 2010; Xu et al., 2015) with BOLD fMRI and broadband sound stimulation. In the remainder of this paper, BOLD fMRI will be referred to as fMRI. Note that chronic continuous hypoxemia, the situation at high altitudes, will not be directly examined. This study will enhance our understanding of central auditory processing after chronic hypoxia and facilitate future auditory studies of hypoxia conditions.

Methods

Animal subjects

All aspects of this study were approved by the animal ethics committees of the City University of Hong Kong, the Chinese University of Hong Kong, and the University of Hong Kong. Our group has extensive experience conducting investigations with rodent subjects, including investigations of chronic intermittent hypoxia (CIH) (Xie et al., 2010; Xu et al., 2015) and the central auditory system using functional magnetic resonance imaging (fMRI) (Cheung et al., 2012a, 2012b; Gao et al., 2015a, 2014, 2015b; Lau et al., 2015a, 2013, 2015b; Zhang et al., 2013). Sixty days old (P60) male Sprague-Dawley rats (N=26) were employed in this study. Subjects first underwent seven days of CIH treatment (CIH subjects) or sham treatment (controls). During this time, subjects were weighed daily and their behavior and food intake were qualitatively monitored. On the 7th day, arterial partial pressure of oxygen (PO_2) and oxygen saturation (SO_2) were measured from five subjects in each group. On the 8th day, fMRI was performed with sound stimulation on eight subjects per group. Separate subjects were employed for oxygen measurements and fMRI as the oxygen measurement procedures were invasive. Subjects were sacrificed after oxygen measurements or fMRI. Fig. 1 illustrates the experimental timeline for each subject.

Chronic intermittent hypoxemia (CIH) treatment

The chronic intermittent hypoxemia procedures in this study were adapted from our recent obstructive sleep apnea (OSA) studies (Xie et al., 2010; Xu et al., 2015). Subjects were placed in custom gas chambers (46×20×22 cm^3) at P60 from 9 am to 5 pm for seven days. The content of the air in the chamber was controlled by an oxygen profiler (Oxycycler model A48XOV; Reming Bioinstruments). For CIH subjects, the oxygen content inside the chamber was cycled between 10% and 21% with 90 s period. For controls, the oxygen content was kept at 21%. After the 8 h of treatment, both groups were returned to standard cages with normal room air. PO_2/SO_2 measurements and fMRI took place after the 7 day treatment period. See Fig. 1 for a description of the treatment timeline. In addition to regulating oxygen, the profiler also controlled nitrogen content in the chamber and humidity was maintained at 40–50%. The temperature inside the chamber was maintained between 22–24 °C and the CO_2 content was monitored. Subjects received ad libitum access to food and water and were housed in a 12 h light/dark cycle. The above CIH model mimiced the repeated episodes of airway obstruction in OSA without the complication or interference by sleep deprivation and fragmentation. The protocol was based on well reported rodent models of sleep apnea, which aimed to reproduce the overall cumulative hourly oxygen desaturation patterns routinely observed in moderately severe OSA patients (Gozal et al., 2001; Xu et al., 2004).

Arterial blood oxygen

Arterial PO_2 and SO_2 were measured on the 7th CIH treatment day with the subjects in the gas chamber. This measurement must be done in the low oxygen environment as PO_2 and SO_2 rapidly recover after the subject is returned to normal atmosphere. The subject was anesthetized using chloral hydrate and fixed on an operation plate. After the abdominal aorta was uncovered by surgery, the subject together with the operation plate, was taken back into the chamber for at least