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Brief communication

Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea

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Abstract

Background and purpose: Obstructive sleep apnea (OSA) is associated with intermittent hypoxia and cognitive decrements. As the hippocampus is particularly susceptible to hypoxia, we hypothesized that it may show biochemical abnormalities, and they may relate to apnea severity.

Patients and methods: Eight males with OSA and five age-matched controls underwent neurocognitive testing before and after polysomnography and proton magnetic resonance spectra were obtained from the left hippocampal area of all subjects.

Results: In the left hippocampal area, *N*-acetyl-containing/creatine-containing compounds was significantly increased in OSA ($P=0.04$). Inspection of these compounds with respect to the water resonance indicated that this was most likely due to a decrease in creatine-containing compounds rather than any change in *N*-acetyl-containing compounds. Lower levels of hippocampal creatine-containing compounds were correlated with worse OSA severity and neurocognitive performance.

Conclusions: We suggest the changes in creatine levels in the hippocampal area represent adjustments to brain bioenergetics, similar to those seen in ischemic preconditioning, and may reflect the different susceptibility of these tissues to hypoxic damage in OSA.

Keywords: Obstructive sleep apnea; Magnetic resonance spectroscopy; Hippocampus; Creatine; Neurocognitive deficits

1. Introduction

Obstructive sleep apnea (OSA) is characterized by both repetitive asphyxia and sleep fragmentation leading to neurocognitive decrements and vascular disease [1]. There are varying levels of daytime dysfunction reported in patients with OSA [1], including memory impairment. The hippocampus is extremely vulnerable to intermittent hypoxic insult in animal models [2]. Recently, hippocampal grey matter volumes were decreased in association with OSA [3], suggesting this vulnerability translates to humans.

To examine this further, we studied the hippocampal area of eight subjects with OSA and five controls using ^{1}H magnetic resonance spectroscopy (MRS) and a neurocognitive test battery, immediately following overnight polysomnography (PSG).

2. Methods

This study complied with NHMRC guidelines on human research and was approved by institutional Ethics

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Committees. Informed consent was obtained from all participants. Eight OSA subjects (mean age 48.7 years (range 41.1–56.4 years)) were recruited from sleep clinics at St Vincent's Clinic and Royal North Shore Hospitals in Sydney, Australia. Selection criteria included both a respiratory disturbance index of >15 and a minimum oxygen desaturation of $\leq 90\%$ ($Sa0_2 < 90\%$). Five control subjects (mean age 50.6 years (range 40.7–60.4 years)) were matched with OSA subjects as closely as possible by age and occupation.

2.1. Study protocol

16:00 hours: all subjects completed a baseline neurobehavioral assessment battery (16:00 to 18:00).

18:00 hours: subjects were set up for PSG and continuous monitoring occurred from 22:00 to 06:00.

07:00 hours: subjects underwent MRI/MRS.

08:00 hours: repeat neurobehavioral assessment battery (08:00–09:30).

Subjects were asked not to consume any caffeine or alcohol on the day of examination until ~10:00 hours the following morning.

2.2. Neurocognitive test battery

The neurobehavioral assessment battery [4] is a standardized and validated procedure which measures daytime performance. Two objective processing tasks are reported here. The Psychomotor Vigilance Task (PVT) [4] measures sustained focused attention and is a 10-min paced reaction time test, where increasing sleepiness is associated with increased reaction times. The Digit Symbol Substitution Task (DSST) is a computerized version from the standardized Wechsler Adult Intelligence Scale Revised, which assesses processing speed, coordination and working memory [5]. Previous researchers suggest that it is the combination of working memory and speed of information processing which best indicates an individual's ability to learn new information [6], as measured in the DSST.

2.3. Polysomnography

A standard set-up was used for PSG. EEG, eye, leg, chin, abdominal and thoracic movement, nasal pressure flow and oxygen desaturation were measured and scored as described previously [7].

2.4. Magnetic resonance

All magnetic resonance imaging and spectroscopy was performed on a GE SIGNA 1.5T magnet. True axial or coronal slices (FLAIR or T2, 5 mm interleaved) were used to screen for CNS abnormalities and for the volume of interest, which was manually placed to encompass an area of mostly the left hippocampus [8] (average voxel size $1.2 \times 1.2 \times 1.0$ cm). ^{1}H MRS spectra were obtained using the PRESS pulse sequence (echo time = 136 ms, repetition time = 1500 ms). Spectra were processed using jMRUI (version 1.0) as described previously [9] and lineshapes fitted to resonances of NA (*N*-acetylaspartate, a marker of neuronal integrity, with a small contribution from *N*-acetylaspartylglutamate), Cho (indicates membrane turnover and/or density and is a composite peak arising from glycerophosphocholine and phosphocholine with a small contribution from free choline) and a composite peak arising from the *N*-methyl resonances of creatine and phosphocreatine (Cre), a measure of cell bioenergetics (Fig. 1A and B). In addition, a [3] Lorentzian lineshape was fitted to the resonance arising from water in the spectrum without water suppression. Results were expressed as peak ratios, and as concentrations relative to the water resonance (expressed as means (standard deviations) in arbitrary units, without correction for relaxation or number of scans).

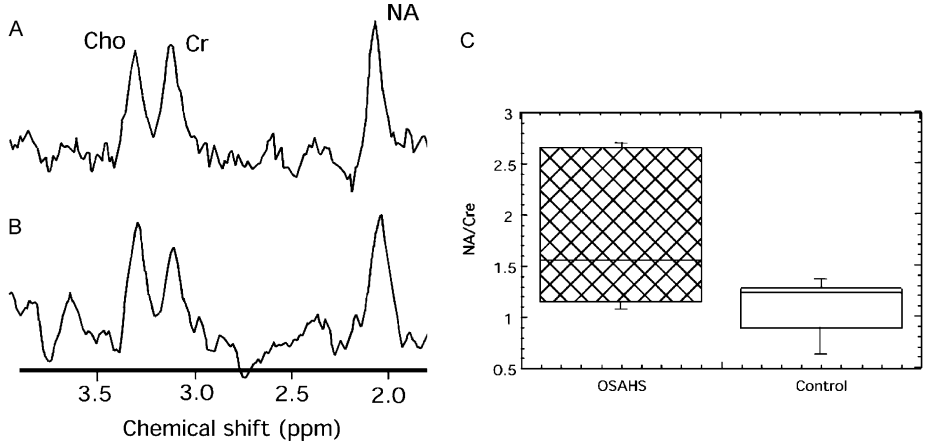

Fig. 1. T2-weighted magnetic resonance spectral acquisition from the left hippocampal area: (A) Control hippocampal area. (B) OSA hippocampal area. (C) Hippocampal area NA/Cre OSA group and control group; the box plot shows the inter-quartile range and the median, whiskers show the range except where there are outliers. *Abbreviations*: Cre, creatine-containing compounds; NA, *N*-acetyl-containing compounds.

Table 1
Indices of OSA and group differences

	Median OSA	OSA IQR	Median controls	Controls IQR	Mann–Whitney *P* value
Age	47.0	15.75	51.75	15.75	>0.62
BMI	30.8	4.63	25.0	3.14	<0.003
TRDI	44.85	43.13	4.0	4.5	<0.002
NREM RDI	45.1	46.62	2.8	5.3	<0.002
REM RDI	31.1	52.1	4.0	4.6	<0.03
Minimum O_2 desaturation	76.5	26.25	90.0	2.75	<0.002
Average O_2 desaturation	11.5	8.0	3.0	2.25	<0.002
Mean apnea hypopnea duration	25.85	12.5	19.0	4.5	>0.28
%Total time spent in apnea	34.5	43.4	1.9	2.64	<0.002
Arousal index	50.3	42.7	9.7	5.75	<0.002
SaO_2 > 90%	1.12	222.8	0.01	0.1	<0.02

Abbreviations used: IQR, interquartile range; BMI, body mass index; TRDI, total respiratory index; NREM RDI, non-rapid eye movement respiratory disturbance index; REM RDI, rapid eye movement respiratory index; SaO_2 90%, oxygen saturation less than 90%.

2.5. Statistics

Statistical analysis was performed using SPSS for Windows (Version 11.5). Data for each variable were expressed as medians with inter-quartile range (IQR). Group differences were examined using the Mann–Whitney test. Associations between variables were quantified using the Spearman rank correlation coefficient; $\alpha = 0.05$ was considered significant.

3. Results

There were clear differences between OSA subjects and controls in all sleep and breathing variables (Table 1). BMI, but not age, was significantly different between the OSA and control groups.

3.1. ^1H magnetic resonance spectroscopy

Hippocampal area NA/Cre (Fig. 1C) was significantly increased ($P = 0.04$) in the OSA group (1.73 (1.46)) compared with the control group (1.25 (0.56) arbitrary units). This increased ratio was more likely due to a decrease in hippocampal creatine (OSA 6.94 (6.13); control 9.62 (3.79) arbitrary units; ($P = 0.06$)) rather than to an increase in hippocampal NA (OSA 9.94 (6.78); control mean 9.06 (2.86) arbitrary units ($P = 1.0$)).

3.2. Relationship between brain metabolites and OSA indices

In all subjects, the hippocampal area NA/Cre was significantly and positively correlated with arousal index (r_s 0.68; $P = 0.01$; $N = 13$) and BMI (r_s 0.68; $P = 0.01$; $N = 13$) while total respiratory disturbance index (r_s 0.51; $P = 0.07$; $N = 13$), non-rapid eye movement respiratory disturbance index (r_s 0.54; $P = 0.06$; $N = 13$), average O_2 desaturation (r_s 0.54; $P = 0.06$; $N = 13$), and percentage total time spent in apnea (r_s 0.52; $P = 0.07$; $N = 13$), showed trends towards significance. All correlations lay in the same direction, with increased OSA-severity relating to decreased Cre levels. Cre levels were also found to correlate negatively with BMI (r_s −0.65; $P = 0.02$; $N = 13$), and a trend was found with the arousal index (r_s −0.49; $P = 0.09$; $N = 13$).

3.3. Relationship between brain metabolites and neurocognitive performance

Changes in Cre levels were found to correlate with worsening neurocognitive performance in the hippocampal area in the OSA group. Decreased vigilance or increased number of lapses in the PVT was associated with decreased Cre in the afternoon (r_s −0.75; $P = 0.03$; $N = 7$) and morning (r_s −0.84; $P = 0.02$; $N = 7$) while a negative correlation with NA was significant in the morning only (r_s −0.77; $P = 0.04$; $N = 8$). In the control group, increased hippocampal Cre correlated with evening and morning performance improvements in the PVT worst reaction times (r_s 0.90; $P = 0.04$; $N = 5$), but only morning improvements in the DSST reaction time (r_s 0.90; $P = 0.04$; $N = 5$) and in the DSST number of correct responses (r_s 0.90; $P = 0.04$; $N = 5$).

4. Discussion

Using ^1H MR spectroscopy we observed a major change in brain neurochemistry. The Cre resonance decreased in the hippocampal area in diagnosed OSA subjects compared with control subjects, and was associated with worsening neurocognitive performance. It is perhaps not surprising that the Cre resonance should be sensitive to intermittent hypoxia. Creatine plays a pivotal role in brain energy homeostasis and acts in concert with multiple ATP-producing and requiring reactions as a buffer for high-energy phosphate bonds. Creatine has neuroprotective

properties [10] and enhances neurocognitive abilities [11]. Levels of hippocampal Cre respond to hippocampal exercise [12], suggesting turnover is dynamic, at least on the week time scale. The association of decreased Cre with OSA severity and increased reaction times in the PVT seen in this study indicate that the reduction in hippocampal Cre may be detrimental, and that OSA, with oxygen deprivation, is associated with loss of hippocampal function.

The hippocampal area of the brain is metabolically active and is highly susceptible to hypoxic insult. Contrary to expectations, given the reported deficit in hippocampal gray matter in OSA [3,13], we found no significant group difference in hippocampal NA levels, although it was apparent from the correlation between NA levels and PVT lapses that worsening neurocognitive performance was associated with decreasing NA levels. Previous research has established how active neurogenesis in the hippocampus allows for at least partial recovery from injury including intermittent hypoxia [14]. Although an earlier investigation of MRS in OSA reported an association between the NA/Cho ratio and apnea severity [15], this study was in periventricular white matter and may be more reflective of changes in axonal myelination. Given the low number of subjects and higher inter-individual variability within the OSA subjects, a larger study is needed to clarify these questions, as well as to further test the underlying causes of the correlations between brain metabolite levels and physiological and psychological parameters.

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