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Plasma Orexin Levels Related to Altered Brain Activity During Abstinence in Patients with Alcohol Dependence

Jianshe Pan[1], Guangdong Chen[2], Peiwei Shan[2], Ce Chen[2], Deguo Jiang[2], Lina Wang[3], Gongying Li[4], Min Chen[4], Chuanjun Zhuo[2,*], Tao Fang[5,*], Haiping Yu[2,*]

[1]Department of Psychiatry, Wenzhou Kangning Hospital, Wenzhou, Zhejiang Province, China; [2]Department of Psychiatric-Neuroimage Center, Radiology Center, Wenzhou Seventh People's Hospital, Wenzhou, Zhejiang Province, China; [3]Psychiatric-Neuroimaging-Genetics-Comorbidity (PNGC) Laboratory, Tianjin Anding Hospital, Nankai University Affiliated Anding Hospital, Tianjin Mental Health Center, Tianjin, China; [4]Department of Psychiatry, School of Mental Health, Jining Medical University, Jining, Shandong Province, China; [5]Laboratory of Neurology-Psychiatry Biological-Neuroimaging (NPBI-Lab), Tianjin Fourth Center Hospital, Tianjin, China

**These authors are co-corresponding authors to this work.*

ABSTRACT

Objectives: In vivo studies have correlated brain activity with alcohol-seeking behavior, while clinical studies have identified altered brain activity in patients with alcohol dependence (AD) even during abstinence. We aimed to explore the relationship between plasma orexin levels, brain activity, and alcohol-craving scores in patients with AD.

Methods: In this pilot study, we evaluated 24 male patients with AD in remission and 25 male controls. Alcohol craving was assessed using the Obsessive Compulsive Drinking Scale (OCDS). An adapted MRI technique was used to assess global functional connectivity density (gFCD), and plasma orexin concentrations were measured by radioimmunoassay. Associations were analyzed by the Pearson correlation.

Results: Plasma orexin levels in AD patients in remission were significantly higher than those in the controls. OCDS scores correlated to orexin concentrations ($r = 0.47$, $P < .05$). Compared to the controls, all AD patients demonstrated reduced gFCD, primarily in the frontal, temporal, and parietal lobes, and increased gFCD in the accumbens nuclei and posterior insular cortex. Mean gFCD values in the accumbens nuclei significantly correlated to craving scores ($r = 0.55$, $P < .05$). Although assessed during abstinence, the reward circuits in AD patients exhibited increased activity. Orexin levels correlated to increased activity in the accumbens nuclei and craving scores.

Conclusions: The potential clinical utility of plasma orexin levels to assess the risk of relapse in AD patients in treatment and prevention programs deserves further study.

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INTRODUCTION

Alcohol abuse has been identified as the leading cause of disease burden among persons between the ages of 15–49 worldwide.[1] It is crucial to develop prevention and treatment modalities for patients with alcohol dependence (AD), a prevalent diagnostic subtype of alcohol use disorders (AUD).[2,3] Although naltrexone, topiramate, baclofen, and other medications have been used to prevent relapse in patients with AD, results have been disappointing.[4,5] Basic and clinical research efforts to identify fundamentally new approaches to prevent relapse are needed.[6] The integration of a clinical biomarker into prevention programs would help to monitor the risk of relapse and would support novel strategic approaches.

Orexinergic neurons release multiple neurotransmitters and neuromodulators[7] (including dynorphin) that exert an inhibitory effect on motivation and reward centers. This suggests that the orexinergic system may provide therapeutic targets to prevent alcohol-seeking behavior in patients with AD by modulating the functional activity of the reward system.[8,9] In addition, we propose that plasma orexin assays may have clinical utility in monitoring the risk of alcohol-seeking behavior in AD.

Previous studies have reported abnormal brain activity in patients with AUD and AD. These include ventral visual pathway-cerebellar circuit deficits, indicated by abnormal functional connectivity density (FCD).[10,11] Increased

Corresponding author: Chuanjun Zhuo or Tao Fang or Haiping Yu, e-mail: chuanjunzhuotjmh@163.com or fangtao5102@163.com or yuzhengyu123456@163.com

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functional connectivity between the nucleus accumbens reward center and the visual cortex was identified in adolescents with positive family histories of AUD.[12] Alcohol craving (a core symptom of AD) has been associated with altered thalamic caudate connectivity[13] and abnormal brain activity.[14]

The studies mentioned above indicate that AD relapse is associated with altered brain activity and orexin signaling pathways. Discovering the link between orexinergic activity and brain function can identify new therapeutic targets to sustain long-term abstinence and reduce the burden of AD. Global functional connectivity density (gFCD) has been used to assess brain connectivity and regional brain metabolism.[15] In this study, we aimed to examine the relationships between plasma orexin levels, gFCD, and alcohol-craving symptoms in patients with AD.

METHODS

Participants

Our study protocol was reviewed and approved by Wenzhou Seventh People's Hospital Ethics Committee (approval date: March 2, 2016). The inclusion criteria were: (1) AD diagnosed by the Structured Clinical Interview for DSM-IV, (2) age ≥18 and ≤35 years, (3) abstinence for at least 4 weeks, defined as no consumption of any alcohol-containing drink for at least 4 weeks, and granting informed consent to undergo breath analyzer testing at 6-h intervals during the study (derived from the criteria of National Institute on Alcohol Abuse and Alcoholism [NIAAA]), (4) stable mental health for at least 4 weeks (defined as the diagnostic exclusion of anxiety, mood disorder, and sleep disorder, while simultaneously not having a history of rage or making verbal or physical threats to others), and (5) full comprehensive insight (defined as having knowledge of one's illness, an awareness of one's symptomatic presentations, and an understanding of the need for treatment).[16] Participants were excluded if they had histories of other substance abuse; head trauma, seizure, or other neurological disorders; mental retardation; other psychological disorders; or violent behavior in the past year. Between July 2018 and July 2019, 60 male patients were enrolled. Healthy controls were recruited from the hospital staff. Signed written informed consent was acquired from all participants, or when appropriate, their legal guardians.

Alcohol Dependence Assessment

The Alcohol Use Disorder Identification Test (AUDIT) and the positive Alcohol Expectancy (AE) scale were used to assess current AD severity.[17] Alcohol craving was assessed by the Obsessive Compulsive Drinking Scale (OCDS),[18], has 14 items that are scored from 0 to 4. Participants recorded the mean intensity, maximum intensity, and frequency of alcohol-craving experienced during the preceding week on a 100 mm visual analog scale.

MRI Data Acquisition

MRI was performed with a 3T GE Discovery MR750 scanner (General Electric, Milwaukee, WI, USA) with an eight-channel phased-array head coil. Participants assumed a supine position and remained stationary during the scan. Whole-brain resting-state fMRI (rs-fMRI) recorded blood oxygen level-dependent signals using a gradient-echo-planar imaging sequence. Parameters were set as repetition time (TR) = 2000 ms; echo time (TE) = 45 ms; slice number = 32; slice thickness = 4 mm; gap = 0.5 mm; field of view (FOV) = 220 × 220; matrix size = 64 × 64; and flip angle (FA) = 90°. Structural images were obtained using a high-resolution 3D Turbo-Fast Echo T1WI sequence. The parameters were set as TR/TE = 8.2/3.2, slice number = 170, slice thickness = 1 mm, no gap, FOV = 256 × 256, matrix size = 256 × 256, FA = 12°. All scans were obtained by parallel imaging using the sensitivity encoding (SENSE) technique (SENSE factor = 2).[19]

Data Processing

Statistical Parametric Mapping 12 (SPM12, UK) was used to process rs-fMRI data. The first 10 volumes of scans were discarded and the remainder were corrected for slice-timing and motion artifacts. Head translation movement was set at less than 2 mm, and rotation was set at less than 2°. The Friston 24-parameter model was used to cancel head motion effects. Data were regressed out when the frame-wise displacement was more than 0.5. Datasets were filtered with band-pass frequencies between 0.01 and 0.08 Hz. Individual structural images were co-registered to the mean functional image, and the transformed structural images were co-registered to the Montreal Neurological Institute (MNI) space using a linear registration. The motion-corrected functional volumes were spatially normalized to the MNI space using parameters estimated during linear co-registration. Finally, the functional images were re-sampled into 3-mm cubic voxels for analysis.[20]

Calculation of the gFCD

FCD maps were spatially smoothed by Gaussian kernel (6 × 6 × 6 mm^3) analysis to reduce differences between different subjects. FCD was then calculated using an in-house Linux script.[21] Functional connectivity between voxels was assessed by Pearson's linear correlation (correlation coefficient > 0.6).[21] The gFCD within the cerebral gray matter at any given voxel (×0) was calculated as the total number of functional connections. A growth algorithm was applied between ×0 and all other voxels. The gFCD was divided by the mean of the qualified voxels to increase the normality of distribution.[22]

Radioimmunoassay

Plasma orexin levels were measured at 7 a.m. using a modified radioimmunoassay (RIA, Peninsula, San Carlos, CA, USA). A 1-ml plasma specimen from each subject was analyzed using preconditioned RP-18 columns (Merck, Darmstadt, Germany) and washed with ethanol/acetic acid. After elution, the samples were dried and reconstituted in an RIA buffer. Bound and unbound antigens were separated.[23]

Statistical Analysis

Pre- and post-treatment differences in gFCD were corrected by family-wise error control.[24] The Student's *t*-test was used to detect differences in plasma orexin levels between the 2 groups. Pearson correlation was used to evaluate the associations of plasma orexin levels, craving scores, and gFCD. *P* values <.05 were considered statistically significant.

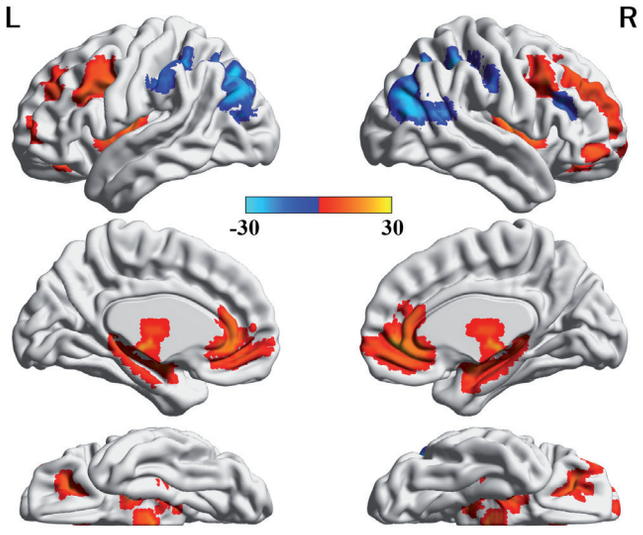

Figure 1. gFCD differences between patients with AD and healthy controls.

RESULTS

We evaluated 24 patients and 25 healthy controls. Social-demographic and clinical characteristics of subjects are listed in Table 1. Compared to controls, the AUDIT, AE, and OCDS scores were higher in AD patients. Plasma orexin levels in AD patients in remission were significantly higher than in healthy controls (Table 1). By correlation analysis, we observed a significant association between OCDS scores and orexin levels ($r=0.47$, $P < .05$) (Table 1). Compared to controls, all AD patients demonstrated reduced gFCD, primarily in the frontal, temporal, and parietal lobes; and increased gFCD in the accumbens nuclei and posterior insula (Figure 1). The mean values of gFCD in the accumbens nuclei were significantly correlated to plasma orexin levels ($r=0.55$, $P < .05$) (Figure 2) and craving scores.

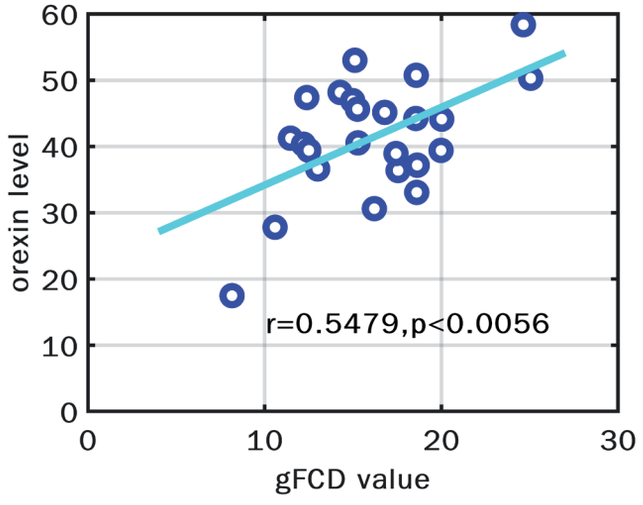

Figure 2. gFCD peak value in nucleus accumbens correlated with plasma orexin in the patients with AD.

DISCUSSION

To our knowledge, this study is the first to evaluate relationships between craving scores, plasma orexin levels,

Table 1. Social-demographic and Clinical Characteristics of Patients With AD and Healthy Controls

Variable	AD Patients ($n=24$)	Healthy Controls ($n=25$)	*t*	*P*
Age (years)	28.4 ± 4.5	28.5 ± 3.8	0.230	.777
Education level (years)	12.5 ± 5.5	16.5 ± 3.5	7.130	<.001
Illness duration (years)	6.5 ± 3.8	N/A	N/A	N/A
AUDIT score	5.2 ± 2.1	1.8 ± 0.5	3.076	<.001
AE score	105.2 ± 23.5	38.5 ± 3.5	11.230	<.001
OCDS score	31.81 ± 2.45	14.6 ± 2.0	3.632	<.001
Orexin (pg/ml)	15.2 ± 1.0 CVs:4.50~17.30	2.6 ± 0.8 CVs:10.75~8.20	10.450	<.001

AD, alcohol dependence; AUDIT, alcohol use disorder identification test; AE, alcohol expectancy; OCDS, Obsessive Compulsive Drinking Scale; CVs, coefficients of variation.

and brain activity in AD patients. AE and OCDS scores were significantly higher in AD patients during remission than those in the controls, which suggests that patients remain at a higher risk of relapse for a prolonged duration. This finding is consistent with a previous report that AD relapse rates can exceed 80% within one year.[25]

In a previous study, Ziółkowski et al.[13] reported that alcohol-dependent patients had significantly greater orexin blood concentration than controls. After 4 weeks of treatment for relapse prevention, the blood orexin level decreased significantly to a value similar to that in the control group.[26] Jupp et al.[27] reported that the orexin receptor antagonist SB-334867 significantly attenuated cue-induced reinstatement in alcoholic animal models.[27] James et al.[28] also confirmed the role of orexin in modulating motivational drug-seeking behavior, and highlighted that an orexin receptor antagonist has been approved for treating AD.[28] All these previous studies, combined with our present findings, suggest that plasma orexin levels are directly related to alcohol-craving levels, and that the reduction of orexin levels may prevent the relapse of AD.

Previous studies have reported that brain imaging biomarkers can predict relapse in alcohol addiction. For example, Volkow et al.[29] reported that vmPFC/ACC and the precuneus, the central nodes of the default mode network (DMN), play a key role in the relapse of AD, and that hyperactivity in the DMN predicts relapse.[29] Previous studies demonstrate the interplay of the DMN with the reward system that subsequently exacerbates the relapse risk for AD.[30] In the present study, we observed that increased gFCD in the posterior insular cortex and accumbens nuclei, which are pivotal components of the reward system, link the previous findings with our results, and all suggest that brain imaging biomarkers can be used to predict the relapse of AD.[31-36]

We also observed that all AD patients exhibited reduced gFCD primarily in the frontal, temporal, and parietal lobes, showing that long-term alcohol dependence is accompanied by major functional impairments of the neuroanatomic regions that are central components of the processing networks of cognition, executive ability, and emotion, the key determinants of quality of life.[37-41] Our findings are consistent with those of previous studies that also reported brain structural and functional abnormalities in AD patients.[31,34-37]

Third and significantly, we observed the correlations between plasma orexin levels, gFCD alterations, and craving scores. These findings converged to strengthen our understanding of the relationship between AUD, orexin signaling,[37,29] and brain activity.[11] The findings of our pilot study integrate neurobiological mechanisms for the relapse risk in AD patients, and also suggest that measurements of plasma orexin levels may have clinical utility as biomarkers to quantify those risks.

Limitations

There were several limitations of our study. First, the sample size of AD patients was relatively small, which limits the strength of our conclusions. A larger cohort study is needed to further validate our findings. Secondly, we regressed out many variables in investigating brain activity that specifically related to craving. In a future study, we will establish an improved method to evaluate a large cohort. Thirdly, we only focused on the regional functional activity of the reward system. In a future study, we will comprehensively evaluate the functional activity of the entire brain in AD patients.

CONCLUSION

The reward circuits in AD patients exhibited increased activity compared to controls even after 4 weeks of abstinence, and correlated with plasma orexin levels and craving scores. The correlation of plasma orexin levels to both craving scores and gFCD underscores the potential clinical utility of the plasma orexin level as a biomarker to monitor AD patients to prevent relapse. The potential role of a diagnostic assay using a readily available clinical specimen deserves further study.

Ethics Committee Approval: Ethics committee approval was received from the Wenzhou Seventh Peoples Hospital Ethics Committee (IRB:2016-25).

Informed Consent: Written informed consent was obtained from all participants who participated in this study or when appropriate, from their legal guardians.

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