Relationship Between Cognitive Impairments and Serum Orexin Levels in Epilepsy Patients

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Abstract

Objective: Recent studies on neurodegenerative diseases have indicated that Orexin A plays a role in cognitive impairment. Furthermore, animal studies have demonstrated that Orexin A enhances synaptic plasticity in the hippocampus. The present study aimed to investigate the potential effect of orexin A on cognitive decline in patients with epilepsy.

Methods: This study included patients with epilepsy (patient group), including those with idiopathic generalized epilepsy (IGE subgroup) (n=24) and mesial temporal lobe epilepsy (mTLE subgroup) (n=17), and healthy controls (control group) (n=27), all aged 18-65 years. The Wechsler Memory Scale (WMS) visual memory subtest and Oktem Verbal Memory Processes Test (OVMPT) (15-word Turkish verbal learning memory test) were administered to all participants. Serum Orexin A levels were measured using enzyme-linked immunosorbent assay.

Results: The mean Orexin A level in the control group was 25.84±14.65 pg mL^{-1}, versus 24.57±12.50 pg mL^{-1} in the IGE group and 23.01±12.86 pg mL^{-1} in the mTLE group. There were no significant differences in the Orexin A level between any of the groups/subgroups. Moreover, no significant correlation was observed between the Orexin A level, WMS visual memory subtest, and OVMPT scores.

Conclusion: Our findings showed no association between the Orexin A level and cognitive impairment in patients with epilepsy. Further studies are needed to clarify the complex role of Orexin A in cognitive function.

Keywords: Cognitive, epilepsy, Orexin A

INTRODUCTION

Epilepsy is a chronic disease of the central nervous system (CNS) characterized by a variety of recurrent and unpredictable seizures caused by an imbalance in neuronal electrical activity.[1] Epilepsy is one of the most common neurological diseases in the world, with an estimated prevalence of 6.38 per 1000 person.[2,3] Cognitive impairment is frequently observed in patients with epilepsy and is often characterized by mental slowing, memory disorders, and attention deficit.[4]

Orexin A is synthesized by a cluster of neurons located in the lateral hypothalamus and perifornical area.[5] Orexin neurons are multitasking neurons that regulate several vital body functions, including sleep/awake states, eating behavior, energy homeostasis, reward systems, cognition, and mood.[6]

Animal studies have indicated that the orexinergic system might increase hippocampal neurogenesis, which is known to affect learning and memory positively. These studies revealed that orexin/ataxin-3 transgenic mice lacked long-term social memory and that nasal administration of exogenous Orexin A restored social memory and increased synaptic plasticity in the hippocampus.[7] Orexin A has also been shown to enhance the long-term potentiation (LTP), which plays a critical role in attention and memory.[8] It was reported that local dentate gyrus perfusion with Orexin A in rats under anesthesia increased LTP and strengthened the link between structural and functional hippocampal plasticity. It was also shown in the same study that providing SB-334867, an orexin 1 receptor (Ox1R) antagonist, to the rats blocked the increase in LTP.[9] A study examining the absence of epilepsy and the orexin system in rats showed that rats with epilepsy had decreased levels of orexin receptor type 1 protein (OX1) compared with rats without epilepsy. The authors suggested that the orexin system is involved in the pathophysiology of epilepsy in patients without epilepsy.[10]

Clinical studies have increased with the occurrence of the importance of the role of Orexin A in narcolepsy in neurological diseases. Recently, various studies have been conducted on several neurological diseases, such as Alzheimer's disease, Parkinson's disease, and stroke.[11-15] A previous study revealed that Orexin increased amyloid-β accumulation and prevented amyloid-β degradation in Alzheimer's disease patients, leading to neurodegeneration and cognitive impairment.[13-15] A review study on stroke showed that the Orexin system improved memory by modulating other neurotransmitters after stroke.[12] However, very few studies have investigated the relationship between Orexin A and epilepsy.[16,17] Few studies have focused on the relationship between seizures and Orexin A; however, the results were inconsistent. Only one study examined the relationship between Orexin A and cognitive impairment in epilepsy patients in 2023 and suggested that lower Orexin A levels in epilepsy patients may be associated with cognitive damage.[18]

In this context, this study aimed to determine whether there is a relationship between Orexin A levels and cognitive impairment in patients with epilepsy using the Wechsler memory scale (WMS) visual memory subtest and Oktem Verbal Memory Processes Test (OVMPT) and to contribute to the literature.

METHODS

Study Design

This study was conducted at the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, İzmir, Turkey, between April 2020 and November 2020. The İzmir Tepecik Training and Research Hospital Ethics Committee approved the study protocol, and all procedures were followed according to the ethical standards outlined in the Declaration of Helsinki (decision no: 3, date: 21.02.2020). Written informed consent was obtained from all participants, and the study protocol, potential hazards, and benefits were explained to all participants.

Participants and Seizure Classification

The study included participants aged between 18-65, followed up for mesial temporal lobe epilepsy (mTLE) and idiopathic generalized epilepsy (IGE) and healthy controls who agreed to participate in the study. The patient sample consisted of patients with epilepsy diagnosed according to the clinical epilepsy diagnosis criteria established by the International League Against Epilepsy (ILAE) in 2014 and followed up in the epilepsy outpatient clinic. IGEs, which include the following four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone, were determined according to the ILAE 2017 classification of epilepsies. mTLE was defined as patients with one of the familial mTLE (FmTLE) or mTLE with hippocampal sclerosis syndromes according to the ILAE 2017 epilepsy classification.

MAIN POINTS

- Orexin A is a multitasking neuropeptide that plays a role in several aspects, including sleep/wake states, eating behavior, and energy homeostasis.
- Animal studies have shown that Orexin A can enhance synaptic plasticity in the hippocampus.
- Recent research on neurodegenerative diseases has revealed that Orexin A plays a role in cognitive function.
- Our findings did not indicate a relationship between cognitive impairment and Orexin A levels in patients with epilepsy.

The exclusion criteria for all participants were as follows: diagnosis of dementia or cognitive impairment, comorbid psychiatric disorders, such as anxiety and mood disorders, concomitant CNS diseases, ongoing use of opioids, and CNS stimulants.

Cognitive tests and Orexin A level measurements were performed after the post-ictal period was over in order not to affect the results in patients with frequent seizures.

Assessment of the Seizure-free State, Drug Sensitivity, and Seizure Frequency

Patients' demographic characteristics, other chronic illnesses, and the medications they have been using were recorded. Patients who could not attain long-term seizure-free status despite receiving ≥2 appropriate antiepileptic drugs alone or in combination were defined as drug resistant according to the ILAE 2010 criteria. The patient group was divided into three subgroups according to the frequency of seizures: rare seizures subgroup: <1 seizures per year; sporadic seizures subgroup: 1 to 11 seizures per year; frequent seizures subgroup: 1 to 4 seizures per month. No patient experienced >4 seizures per month.

Orexin A Measurements

Blood samples to measure serum Orexin A levels were collected 10 mL peripheral blood from each participant between 8:00 and 9:00 a.m., according to the diurnal rhythm. Blood samples were centrifuged (2500 g for 15 min) within 1 h of collection and then kept frozen at -80 °C until assay. Blinded researchers determined serum NFL concentrations for clinical diagnosis. Serum Orexin A levels within the 10-1280 pg mL^{-1} range were measured using enzyme-linked immunosorbent assay method. Blood samples were taken from each participant into a clot-activating tube with a gel separator (BD Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm, NJ, USA).

Statistical Analysis

The collected research data were analyzed using the Statistical Package for the Social Sciences 21.0 (Statistical Product and Service Solutions for Windows, version 21.0, IBM Corp., Armonk, NY, U.S., 2012) software package and MS Excel 2007 (Microsoft Excel 2007, Microsoft Corporation, Redmond, Washington U.S., retrieved from https://office.microsoft.com/excel) software. The normal distribution characteristics of continuous variables, including age, WMS short- and long-term memory scores, OVMPT immediate memory score, maximum learning number, spontaneous recall, total recall, total learning scores, and Orexin A level, were analyzed using the Shapiro-Wilk test. Additionally, the Kruskal-Wallis non-parametric analysis of variance (ANOVA) was used to compare the WMS STMS and OVMPT immediate memory, maximum learning, 40-min. delayed spontaneous recall, and total recall scores between the groups/subgroups (GE subgroup, TE subgroup, and control group). The Bonferroni correction was applied to the paired comparisons. In cases in which one-

way ANOVA revealed a significant difference, post hoc pairwise comparisons were conducted to identify the group/subgroup that significantly differed from other groups/subgroups. The Mann-Whitney U test was used to compare changes in Oexin A level, WMS short - and long-term memory scores, OVMPT immediate memory, maximum learning, spontaneous recall, and total recall scores in patient and control groups with variables of education level, drug sensitivity, and response to treatment. Spearman's non-parametric correlation analysis determined the correlation between the Orexin A level, WMS short - and long-term memory scores, and OVMPT immediate memory, maximum learning, 40-min delayed spontaneous recall, total recall, and total learning scores. Probability (p) statistics of <0.05 indicated statistical significance.

RESULTS

Baseline Characteristics

The study sample consisted of 41 patients aged 18-65 years diagnosed with epilepsy (patient group) and 27 age- and sex-matched healthy controls (control group). Of the 24 patients with IGE, 16 had tonic-clonic epilepsy or tonic-clonic epilepsy+ absence/myoclonic epilepsy, 5 had pure myoclonic epilepsy, and 3 had pure absence epilepsy. The mean age of the patient and control groups was 35.56±12.05 years (range: 18-60 years), and the mean age of the control group was 36.93±12.44 years (range: 19-58 years). In the patient group, 73.2% (n=30) were female, 26.8% (n=11) were male, 58.5% (n=24) graduated from a primary school or had a lower level of education, and 41.5% (n=17) graduated from a high school or had a higher level of education. In the control group, 51.9% (n=14) were female, 48.1% (n=13) were male, 48.1% (n=13) graduated from a primary school or had a lower level of education, and 51.9% (n=14) graduated from a high school or had a higher level of education (Table 1).

Overall, 24 (58.5%) patients had IGE, 17 (41.5%) had mTLE, 33% had frequent seizures, 67% were treatment-resistant, and ≈50% were on a single medication. Participants' demographic and clinical characteristics are shown in Table 1. The mean age at seizure onset was 16.48±12.06 years, and the mean disease duration was 17.27±12.43 years.

Relationships Among WMS Score, Demographic, and Clinical Characteristics

WMS short and long memory scores were analyzed separately by pairwise comparisons among the three subgroups (mTLE, IGE, and control groups). Pairwise comparisons analysis revealed that the WMS visual memory subtest short-term memory scores (WMS-STMS) were significantly lower in the IGE subgroup than in the control group (p=0.015); there were no statistically significant differences between mTLE-IGE and mTLE-control subgroups (p=1.000 and p=0.090, respectively). The results also revealed that the WMS long-term memory scores (WMS-LTMS) were significantly lower in the GE and TLE subgroups than in the control group (p=0.012 and p=0.026, respectively). Still, there was no statistical difference between the IGE and mTLE subgroups in terms of WMS-LTMS scores (p=1.000). All groups' WMS-LTMS and WMS-STMS scores decreased significantly with age (Spearman's correlation coefficient=-0.257, p=0.034 and Spearman's correlation coefficient=-0.277, p=0.022, respectively).

Table 1. Patients' characteristics

	Patient group [n=41 (%)]	Control group [n=27 (%)]
Age*	35.56±12.05	36.93±12.44
Gender (female/male)	30/11 (73.2/26.8)	14/13 (51.9/48.1)
Level of education (≤primary, ≥high school)	24/17 (58.5/41.5)	13/14 (48.1/51.9)
The type of epilepsy		
Idiopathic generalized epilepsy	24 (58.5)	
Tonic-clonic epilepsy±absence/myoclonic epilepsy	16 (39.0)	
Pure myoclonic epilepsy	5 (12.0)	
Pure-absence epilepsy	3 (7.0)	
Temporal lobe epilepsy	17 (41.5)	
Seizure frequency		
Low	16 (39.0)	
Sporadic	12 (29.3)	
Frequent	13 (31.7)	
AED medication		
Monotherapy	20 (48.7)	
Carbamazepine	3 (7.3)	
Valproate	7 (17.1)	
Lamotrigine	6 (14.6)	
Levetiracetam	3 (7.3)	
Oxcarbazepine	1 (2.4)	
Polytherapy	21 (51.3)	
Response to treatment		
Responsive	16 (39.0)	
Drug-resistant	25 (61.0)	

*Mean±standart deviation.
AED: Antiepileptic drugs

The mean WMS-LTMS and WMS-STMS scores in all groups who graduated from a high school or had a higher education level were higher than those who graduated from a primary school or had a lower education level ($p<0.001$ and $p<0.001$, respectively). The WMS-LTMS and WMS-STMS scores of the patients who received monotherapy were significantly higher than those who received polytherapy in the analysis of all epilepsy patients ($p=0.010$ and $p=0.010$, respectively). Additionally, there was no significant difference between the WMS-LTMS and WMS-STMS median scores between the groups based on treatment response or seizure frequency ($p=0.864$ and $p=0.470$, respectively).

The mean OVMPT immediate memory, maximum learning, 40-min delayed spontaneous recall, total recall, and total learning scores were highest in the control group and lowest in the TLE subgroup ($p=0.045$, $p=0.007$, $p=0.001$, $p<0.001$ and $p<0.001$, respectively). Pairwise comparisons analysis revealed that the OVMPT maximum learning and 40-min delayed spontaneous recall scores were significantly lower in the TLE subgroup than in the control group ($p=0.005$ and $p<0.001$, respectively). There was no significant relationship between immediate memory after OVMPT, frequency of seizures, or number of medications used ($p=0.761$, $p=0.198$, and $p=0.279$, respectively). On the other hand, no significant difference was observed between the OVMPT 40-min delayed spontaneous recall scores and response to treatment and the number of drugs used. Still, a negative correlation was revealed with the frequency of seizures. The OVMPT immediate memory and 40-min delayed spontaneous recall scores decreased significantly with age in all groups ($p=0.002$ and $p=0.003$, respectively).

Relationships Between Orexin A Levels and Demographic and Clinical Characteristics

The mean Orexin A level was 23.92±12.52 pg mL^{-1} in the patient group and 25.84±14.65 pg mL^{-1} in the control group. The mean Orexin A level was 24.57±12.50 pg mL^{-1} in the IGE group and 23.01±12.86 pg mL^{-1} in the mTLE group (Figure 1). The patient and control groups did not exhibit any significant differences in terms of Orexin A levels; moreover, there was no significant difference between the IGE and mTLE subgroups in the Orexin A level ($p=0.721$ and $p=0.771$, respectively). In parallel, triple comparisons did not reveal any significant difference in the Orexin A level between the IGE, mTLE, and control subgroups ($p=0.899$).

There was no significant relationship between Orexin A level and age ($p=0.883$) or level of education ($p=0.464$). Orexin A levels did not significantly differ according to the frequency of seizures, response to treatment, and the number of medications used ($p=0.663$, $p=0.062$, and $p=0.006$, respectively). There was also no significant relationship between the Orexin A level and the WMS-STMS and WMS-LTMS scores, and the OVMPT immediate memory, OVMPT total learning, and 40-min delayed spontaneous recall scores ($p=0.251$, $p=0.629$, $p=0.549$, $p=0.550$, and $p=0.0621$, respectively) (Table 2).

DISCUSSION

This study was conducted to determine the role of Orexin A in cognitive impairment in patients with epilepsy. However, the findings revealed that the orexin A level in patients with epilepsy was not correlated with the OVMPT verbal and WMS visual memory test scores. Therefore, there was no relationship between Orexin A and cognitive damage in patients with epilepsy. Additionally, in our study, no significant difference was found between the Orexin A levels of patients with epilepsy and healthy controls. There is a severe shortage of literature on Orexin A and cognitive damage in patients with epilepsy. A study that explored a scientific question similar to ours reached different conclusions. Li et al.[18] conducted a retrospective study investigating the relationship between Orexin A and cognitive damage in 77 patients with epilepsy and 65 controls. In this study, non-specific screening test MMSE scores were used to detect cognitive damage, and MMSE scores in patients with epilepsy were found to be lower than those in healthy controls. They also found that the Orexin A level was lower in patients with epilepsy than in controls. The multivariate analysis concluded that lower Orexin A levels were an independent risk factor for cognitive impairment in epileptic patients. Further studies are necessary to establish the association between the orexinergic system and cognitive impairment in patients with epilepsy.

On the other hand, clinical studies examining the relationship between epilepsy and Orexin A have primarily focused on the relationship between Orexin A and seizure pathophysiology. One of these studies reported that the CSF Orexin A level measured within 48 hours after the seizure was significantly lower in 21 patients than in the control subjects and that patients with recurrent seizures had the lowest Orexin A levels. Based on these findings, the authors suggested that Orexin A deficiency plays a role in the complex pathophysiology of recurrent generalized tonic-clonic seizures and status epilepticus and may be associated with post-seizure somnolence.[17] A study on paroxysmal sleep disorder biomarkers reported that the serum Orexin A level was lower in epileptic children without seizures than in children with parasomnia; however, the Orexin A level increased after a seizure in children who had seizures during polysomnography. The authors of the said study attributed these findings to an increase in the permeability of the blood-brain barrier during an epileptic attack or to the synthesis of Orexin A during seizures due to neuroprotective/anticonvulsant function.[16] In our study, because of these uncertain results, Orexin A samples were collected after the post-ictal period ended in patients with frequent seizures. Our study did not observe a significant relationship between the Orexin A level and seizure frequency under the given conditions.

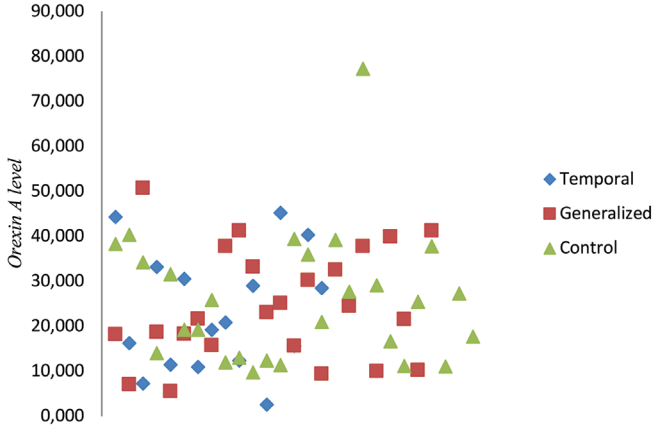

Figure 1. Distribution of Orexin A level by group/subgroup

Table 2. Comparison of Orexin A levels and visual and auditory memory test results among groups/subgroups

	IGE (n=24) Mean±SD Median (IQR)	mTLE (n=17) Mean±SD Median (IQR)	Controls (n=27) Mean±SD Median (IQR)	p value
Orexin A level (pg mL^{-1})	24.57±12.50 pg mL^{-1} 22.38 (20.9)	23.01±12.86 pg/mL^{-1} 20.84 (19.9)	25.84±14.65 pg/mL^{-1} 25.4 (22.9)	0.899
WMS STMS	9.50±3.57 10.0 (5.8)	10.29±2.62 10.0 (5.0)	12.11±1.48 12.0 (3.0)	0.011
WMS LTMS	7.00±3.92 7.0 (6.8)	7.00±2.81 7.0 (5.5)	9.59±2.34 9.0 (3.0)	0.005
OVMPT immediate memory	4.97±1.25 5.0 (1.8)	4.23±1.79 5.0 (2.0)	5.44±1.53 5.0 (1.0)	0.045
OVMPT maximum learning score	14.21±1.38 15.0 (1.0)	13.06±2.13 14.0 (4.0)	14.74±0.59 15.0 (0.0)	0.007
OVMPT 40-min delayed spontaneous recall score	10.58±2.78 10.5 (4.8)	8.35±1.93 9.0 (3.0)	11.59±2.45 12.0 (4.0)	0.001
OVMPT total recall score	13.37±1.81 14.0 (3.0)	11.94±1.39 12.0 (2.0)	14.29±0.99 15.0 (1.0)	<0.001
OVMPT total learning score	115.08±17.33 117.0 (24.5)	95.53±18.45 102.0 (34.5)	122.93±13.5 124.0 (22.0)	<0.001

SD: Standard deviation, IQR: Interquartile range, WMS STMS: Wechsler memory scale short test of mental status, OVMPT: Oktem verbal memory processes test, LTMS: Long-term memory scores, IGE: Idiopathic generalized epilepsy, mTLE: mesial temporal lobe epilepsy

Orexin neurons are predominantly located in the temporal region, and animal studies have revealed that orexin may affect hippocampal neurogenesis. Considering these findings, specific cognitive tests that measure hippocampal function may provide more accurate results than non-specific screening tests. As a matter of fact, in our study, we selected the WMS Visual Memory Subtest and OVMPT, which evaluate hippocampal function. In our study, the OVMPT 40-min delayed spontaneous recall and total recall test scores, which are indicators of long-term verbal memory, were highest in the control group and significantly lower in the mTLE subgroup. In addition, WMS-LTMS scores, which are indicators of long-term visual memory, were substantially lower in the IGE and mTLE subgroups compared with the control group. Memory disorders are expected because TLE originates from the hippocampal and related temporolimbic structures. "Long-term memory" (retrieval of newly learned information) impairment is typically observed in patients with mTLE, and verbal or visual memory impairment is also observed depending on language dominance in the affected temporal hemisphere[19-21] Numerous studies have shown that patients with IGE may have cognitive impairments, such as worsening executive skills, attention deficit, and low general cognitive ability (IQ). However, these studies reported normal functionality in the areas of learning and memory;[22-24] only a few small studies suggested that verbal and visual memory may be affected in patients with IGE.[25-28] The present study revealed that the epilepsy groups (IGE and mTLE) had lower verbal and visual memory scores than the control group. Although our study has a limited sample size, it can be evaluated in line with the literature.

Study Limitations

This study has several limitations. First, the sizes of both the patient and control groups were relatively small and heterogeneous. Second, there is the presence of multiple factors that can affect cognitive test scores, such as epilepsy duration, seizure type, seizure frequency, age at epilepsy onset, use of multiple antiepileptic medications, and side effects, which is also a significant challenge. In our study, half of our patients received monotherapy; the other half received polytherapy. The frequency of seizures differed. These variations may have affected the cognitive function assessment and, consequently, the results. Third, the younger mean age of both the epilepsy patients and control groups may have contributed to the inconclusive results. Last, given that Orexin A affects sleep, autonomic functions, appetite, mood, and the physiological status of patients, the serum Orexin A level might have been affected.

CONCLUSION

Cognitive disorders are common in patients with epilepsy and significantly affect their quality of life. Orexin A, which plays a role in various aspects, such as sleep/awake states, eating behavior, and energy homeostasis, is also believed to be involved in cognitive functions. Animal studies have shown that Orexin A positively affects memory by increasing synaptic plasticity in the hippocampus. Recent research on neurodegenerative diseases has revealed the role of orexin A in neurodegeneration and cognitive impairment. However, studies on Orexin A in patients with epilepsy

are limited, and a clear relationship with cognition has not yet been demonstrated. Our findings showed that the Orexin A level was not associated with verbal or visual memory test scores, indicative of hippocampal function. Therefore, there is no association between Orexin A and cognitive impairment in patients with epilepsy. Further research is required to elucidate the complex role of Orexin A in neurogenesis and epileptogenesis.

Ethics

Ethics Committee Approval: The İzmir Tepecik Training and Research Hospital Ethics Committee approved the study protocol, and all procedures were followed according to the ethical standards outlined in the Declaration of Helsinki (decision no: 3, date: 21.02.2020).

Informed Consent: Written informed consent was obtained from all participants, and the study protocol, potential hazards, and benefits were explained to all participants.

Authorship Contributions

Surgical and Medical Practices: Z.Y., Concept: Z.Y., İ.F.U., Design: İ.F.U., Data Collection or Processing: Z.Y., A.B., Analysis or Interpretation: İ.F.U., A.B., Literature Search: Z.Y., U.Ş., A.S., Writing: Z.Y., İ.F.U., U.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

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