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ORIGINAL ARTICLE

Decreased serum orexin A levels in drug-naive children with attention deficit and hyperactivity disorder

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood and characterized by inattention, hyperactivity, and impulsivity. ADHD is a neurodevelopmental disorder, and its etiology has not yet been determined precisely. Orexin A is thought to play an important role in different forms of learning, memory, and attention. Despite its importance in attention and learning, no study has investigated serum orexin levels in patients with ADHD. In the present study, we aimed to compare serum orexigenic neuropeptides such as orexin A and orexin B, neuropeptide Y, and ghrelin between drug naive children with ADHD and healthy children. Fifty-six drug-naive children with ADHD and 40 healthy controls were enrolled in the study. After comparison of serum orexin A and orexin B, neuropeptide Y, and ghrelin, we found that serum orexin A levels were significantly lower in the ADHD group ($p = 0.001$). Furthermore, serum orexin A levels were compared between ADHD subgroups. Orexin A levels were significantly lower in the inattentive subtype compared with the hyperactive subtype and combined subtype ($p = 0.009$). Our results indicate that orexin A might be a neurobiological etiological factor in ADHD, particularly associated with attention symptoms. The present study is the first to demonstrate decreased serum orexin A levels in drug-naive children with ADHD. Further studies are needed to confirm our results and to show the effects of treatments involving orexin A in patients with ADHD.

Keywords Orexin · Attention · Hyperactivity · Etiology · Neurobiology

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood and is characterized by inattention, hyperactivity, and impulsivity that are not appropriate for the person's age and developmental level. ADHD, a disorder that can lead to extremely important academic, social, and psychiatric problems and is a life-long impairment, is seen in 3–7% of school-age children according to data from the American Psychiatric Association [1]. ADHD is a neurodevelopmental disorder, and its etiology has not yet been determined precisely. Although many abnormalities related to the neurobiological basis of ADHD have been identified in recent years, the connections between genetic, neuronal processes, environmental factors, and their phenotypic manifestations are not well known. Dopamine (DA) and noradrenaline (NA), which is synthesized from dopamine, are important in attention, concentration, and other cognitive functions,

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such as motivation, reward-related behaviors, and alertness. Stimulant drugs, especially those used in the treatment of ADHD, affect both the DA and NA system, and therefore, both systems are prone to impairment [2–4].

Neurotransmitters are modulated by peptidergic activity and are responsible for the regulation of all central nervous system functions. For this reason, research has focused on neuropeptides to understand neuropsychiatric diseases and their treatments in recent years. It has been shown that orexigenic neuropeptides originating from the hypothalamus, such as orexin/hypocretin, neuropeptide Y, and ghrelin, primarily regulate the mesocorticolimbic dopamine system [5]. In addition, anatomical evidence suggests that hypocretin neurons project to different regions of the central nervous system, thereby innervating the noradrenergic locus coeruleus, cholinergic basal forebrain, dopaminergic ventral tegmental area, serotonergic raphe nucleus, and many other brain regions. This mutual interaction of the hypocretin system with other regions of the central nervous system is thought to modulate physiological processes, such as arousal, attention, emotion, reward-related behavior, and food intake through alterations in neurotransmitter function. Disorders in this system may result in significant psychiatric and neurological diseases [6]. Although precise values of orexin, neuropeptide Y, and ghrelin can be detected in cerebrospinal fluid, these chemicals can pass across the blood–brain barrier, and the values that can be detected via plasma can reflect the values in the central nervous system. Moreover, serum orexin levels have been used to support the diagnosis of narcolepsy during daily clinical routine [7–9].

In recent years, a growing amount of empirical evidence has been presented, in addition to the clinical observations on disorders of arousal, reward deficit syndrome (e.g., with abnormal eating behaviors as a natural reward or substance use as an unnatural reward) and ADHD [4, 5]. There are also hypotheses that at least some patients with ADHD have low arousal levels and that the hyperactivity may be a reactive behavior developed to maintain arousal [6]. Research has highlighted the role of the hypocretin/orexin system in altering arousal levels and orientation to natural/unnatural rewards [10]. Neuroanatomically, the level of dopaminergic activity in the nucleus accumbens (NAc) and ventral tegmental area (VTA) appears to play a mediating role in this situation.

Although there have been many studies in the literature on the role of neurotransmitters, such as dopamine, noradrenaline, acetylcholine, and serotonin, in the etiology of ADHD [11, 12], there has been no study investigating whether orexigenic neuropeptides, which play a role in the regulation of these neurotransmitters, have a role in the etiology of ADHD. Finding an association between orexigenic neuropeptides and ADHD and its subgroups will contribute to a better understanding of the disorder at a neurobiological level and enable discussion of new treatment options.

Materials and methods

This study was performed in the Tekirdağ Namık Kemal University Medical School Department of Child and Adolescent Psychiatry and Department of Pediatrics between the dates of June 2016 and October 2017. The inclusion criteria for children in the ADHD group were as follows: diagnosed with ADHD, aged between 6 and 16 years old, and provided approval, received from the child's parents, to be included in the study. The exclusion criteria were as follows: diagnosed with mental retardation, autism, any cognitive disorder or any psychiatric disorders, had any other comorbid medical disease, or being treated by any psychotropic agents. The criteria for the healthy children group were as follows: aged between 6 and 16 years old, had no previous or current diagnosis of a psychiatric disorder, had no current diagnosis of a medical disease, and provided approval received from their parents to be included in the study. Based on the inclusion and exclusion criteria, 56 children who were diagnosed with ADHD and 40 healthy children participated in the study. The present study was approved by the Namık Kemal University Non-Invasive Clinic Research Ethical Committee.

Assessment procedure

The child behavior checklist (CBCL) was administered [13]. The diagnosis of ADHD by a senior child and adolescent psychiatrist was based on the DSM-V criteria [1]. None of the children in the healthy group met the diagnostic criteria for ADHD according to the DSM-V. The clinical assessments proceeded as follows. The Schedule for Affective Disorders and Schizophrenia for school-aged children, lifetime version [14], which was a semistructured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents, was based on clinically diagnosed patients with ADHD and their parents and was used to confirm the diagnosis of ADHD.

Blood collection

After an overnight fast, blood samples were collected from a vein in the antecubital fossa without venous occlusion. The serum was separated and then stored at − 86 °C until biochemical analysis. The participants and their parents were strictly advised not to eat or drink anything during the 12 h before the blood sample was collected. Otherwise, we reassessed the participants who declared that they had not fasted 12 h before the blood sample was taken.

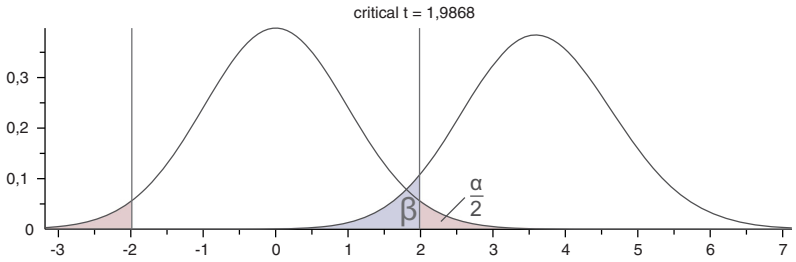

Fig. 1 Power analysis graphic of study

Methodology

Neuropeptide Y assay

Serum neuropeptide Y (NPY) levels were analyzed using an Elabscience ELISA kit, according to the competition principle and microtiter plate separation (Elabscience Biotechnology Co., Ltd. Bethesda, USA). Inter-assay and intra-assay CVs were < 6.61%, respectively. The minimum detectable dose of human NPY is 18.75 pg/mL.

Orexin A assay

Serum orexin A levels were measured using an ELISA kit (Elabscience Biotechnology Co., Ltd. Bethesda, USA). The intra- and inter-assay variabilities of the ELISA kit were < 5.5%. The minimum detectable dose of orexin A was 37.5 pg/mL.

Orexin B assay

Serum orexin B levels were assessed using an ELISA kit (Elabscience Biotechnology Co., Ltd., Bethesda, USA). The intra- and inter-assay variabilities of the ELISA kit were < 10%. The minimum detectable dose of human orexin B is 0.234 pg/mL.

Ghrelin assay

Serum ghrelin levels were measured using an ELISA kit (Thermo Fisher Scientific, Life Technologies, Carlsbad, CA 92008, USA). The intra- and inter-assay variabilities of the ELISA kit were < 8.5%. The minimum detectable dose of human ghrelin is 11.8 pg/mL.

Statistical analysis

Statistical analyses were performed with R 3.5.1, SPSS 23.0, and G*Power 3.1. Power analysis has an important role in experimental design. It was used to determine the sample size required to detect an effect of a given size with a given degree of confidence. For the sample size, power was calculated. For the comparisons, the Kolmogorov–Smirnov test was used to test for normality for each of the categories. The box plots were also used for identifying outliers and for comparing distributions. Nonparametric test statistics were applied because the assumptions were not met. In the nonparametric tests, for two categories, the Mann–Whitney *U* test was used to examine the difference, and for more than two categories, the Kruskal–Wallis test was applied.

Power analysis

The Mann–Whitney *U* test statistic was used as test statistic. According to this test, at $n = 95$, the power was 95% (Fig. 1). The sample size of the study was determined to be $n = 96$, and there was no statistical loss of power. Group sample sizes of 10 and 10 achieve 40% power to detect a difference of 50.5 between the null hypothesis that both group means are 1452.2 and the alternative hypothesis that the mean of group 2 is 1401.8 with known group standard deviations of 56.6 and 73.8 and with a significance level (alpha) of 0.05 using the Mann–Whitney *U* test (Fig. 2).

Results

The numbers of participants in the ADHD and control groups were 56 and 40, respectively. The mean age was 8.66 ± 2.77 years in ADHD group and 7.93 ± 1.98 in control group. Groups were found to be similar in terms of age ($p > 0.05$). There were 17 girls (30.3%) and 39 boys (69.7%) in ADHD group and 12 girls (30%) and 18 (70%) boys in control group (Table 1). Groups were also found to be similar in terms of gender ($p > 0.05$).

As a result of the Kolmogorov–Smirnov test, it was observed that neuropeptide Y, ghrelin, orexin A, and orexin B levels were not normally distributed in the ADHD and HC groups. In addition, the box plot of the serum levels of each of these compounds, shown in Fig. 3a, c, shows the left-skewed distributions, and Fig. 3b shows the right-skewed distribution. For orexin A, 50% percentiles of ADHD and HC groups were far from each other (Fig. 3).

A normal distribution of neuropeptide Y, ghrelin, orexin A, and orexin B was not observed in the ADHD groups. Both the

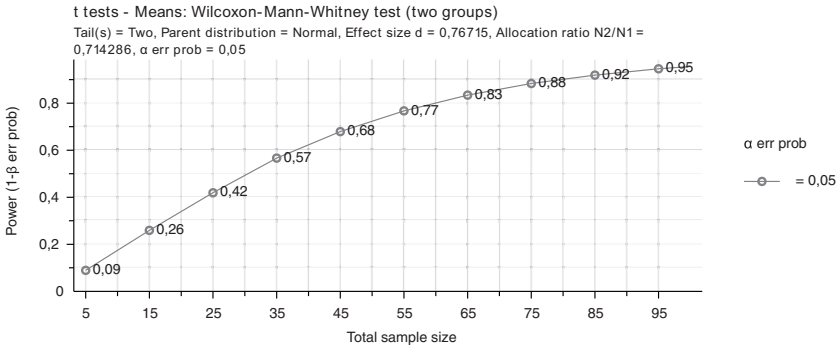

Fig. 2 Demonstration of sample size estimation and power analysis of study

Kolmogorov–Smirnov test and the box plots indicated that serum distributions were skewed (Fig. 4).

Furthermore, a Pearson correlation analysis was performed to identify the correlation between neuropeptide Y, ghrelin, orexin A, and orexin B, as well as CBCL depressive problems (cbcl_dep), CBCL anxiety problems (cbcl_anx), CBCL somatic problems (cbcl_som), CBCL attention problems (cbcl_att), CBCL oppositional defiant problems (cbcl_opp), and CBCL conduct problems (cbcl_con). The correlations of serum levels were low, and the p values of the correlations were not statistically significant ($p > 0.05$) (Fig. 5). The correlations of CBCL scales were moderate or highly correlated, and the p values of the correlations were statistically significant ($p < 0.05$). Overall, between the serum levels (neuropeptide Y, ghrelin, orexin A, and orexin B) and the CBCL scale scores (CBCL depressive problems, CBCL anxiety problems, CBCL somatic problems, CBCL attention problems, CBCL oppositional defiant problems, CBCL conduct problems), correlations were low and not statistically significant.

In the Mann–Whitney U test, there was a significant difference in the 95% confidence level between the ADHD and HC groups in the levels of orexin A ($p = 0.001$). There were no significant differences between the patients and the control group in levels of neuropeptide Y, ghrelin, and orexin B (Table 2).

Lastly, there was a significant difference in the 95% confidence level in orexin A ($p = 0.026$). The inattentive presentation and the hyperactive presentation were the groups that created the differences in orexin A. There were no significant differences in the 95% confidence levels with neuropeptide Y, ghrelin, and orexin B, based on the ADHD presentations (Table 3).

Discussion

ADHD is considered a neurodevelopmental disorder since the DSM-5 was published [1], and from this perspective, ADHD can be considered a psychiatric disorder with a strong neurobiological background [13]. Neurotransmitters are the main actors in the etiologies of various psychiatric disorders. Regarding ADHD, dopamine and noradrenaline have been considered major neurotransmitters in the etiology of ADHD. Thus, the treatment has been based on correcting the function of these two neurotransmitter systems [15–19]. Furthermore, in addition to monoaminergic and amino acid neurotransmitters, there has been attention paid to the neuropeptides with a focus on the etiology of psychiatric disorders.

The effects of neuropeptides as orexin, neuropeptide Y, and ghrelin were initially studied in the mesocortical and mesolimbic dopaminergic pathways and they have been reported to regulate abnormalities in these pathways [20]. After the discovery of the orexins, these neuropeptides have been related to the etiology of hunger, sleep disorders and addiction [21–24]. The role of orexin in attention has been investigated based on the basal forebrain [25, 26]; an orexin-1 receptor antagonist, SB-334867, was shown to disrupt attentional performance while it was administered systemically or directly into the basal forebrain [27]. These results supported the theory that the orexins may be useful for treating cognitive deficits associated with the disruption of cortical cholinergic projections, such as in Alzheimer's disease [28–31]. Orexin-1 receptors have much higher affinity for orexin A than orexin B [22]. In an animal study, administration of orexin, either intravenously or intranasally, improved deficits in primates subjected to sleep deprivation [32]. Additionally, orexin A is thought to play an important role in different forms of learning and memory [33–36]. Based on this accumulation of data, it can be said that orexin A can improve some cognitive deficits based on the different conditions. However, the exact mechanism of action remains unclear. In an experimental study, it has been reported that orexin A enhanced attentional performance via actions in the basal forebrain [20].

In our study, we compared serum orexin A, orexin B, ghrelin, and neuropeptide Y levels between drug-naive children with ADHD and healthy controls. As mentioned in the "Introduction," orexigenic neuropeptides, such as orexin/hypocretin, neuropeptide Y, and ghrelin, primarily regulate the mesocorticolimbic dopamine system. Furthermore, effects in the noradrenergic locus coeruleus,

Table 1 Descriptive statistic. ADHD: attention deficit and hyperactivity disorder, CBCL: the child behavior checklist

	Variables		Number	Percent	$\bar{x}$	Median	s
ADHD group	Age		56		8.50	7.50	2.56
	Gender	Boy	45	80.4			
		Girl	11	19.6			
	ADHD Presentation	Inattentive presentation	16	16.7			
		Hyperactive presentation	7	7.3			
		Combined presentation	33	34.4			
	Neuropeptide Y (pg/mL)		56		629.70	651.08	79.22
	Ghrelin (pg/mL)		56		272.38	169.95	277.88
	Orexin A (pg/mL)		56		1401.78	1410.06	73.81
	Orexin B (pg/mL)		56		6.41	6.55	0.784
	CBCL depressive problems		56		59.96	58.0	8.00
	CBCL anxiety problems		56		59.71	54.0	10.05
	CBCL somatic problems		56		53.50	50.0	6.68
	CBCL attention problems		56		65.87	66.0	7.84
	CBCL oppositional defiant problems		56		61.14	58.50	8.59
	CBCL conduct problems		56		59.78	60.0	8.10
HC group	Age		40		10.75	10.00	2.88
	Gender	Boy	23	57.5			
		Girl	17	42.5			
	Neuropeptide Y (pg/mL)		40		641.05	680.84	78.11
	Ghrelin (pg/mL)		40		280.62	217.12	229.75
	Orexin A (pg/mL)		40		1452.23	1470.88	56.598
	Orexin B (pg/mL)		40		6.61	6.74	0.650
	CBCL depressive problems		40		56.52	56.0	6.18
	CBCL anxiety problems		40		57.20	54.0	6.62
	CBCL somatic problems		40		54.45	50.0	7.38
	CBCL attention problems		40		52.55	51.0	3.80
	CBCL oppositional defiant problems		40		52.75	51.0	3.41
	CBCL conduct problems		40		52.12	51.0	3.70
Total	Age		96		9.43	9.00	2.90
	Gender	Boy	68	70.8			
		Girl	28	29.2			
	ADHD presentation	Inattentive presentation	16	16.7			
		Hyperactive presentation	7	7.3			
		Combined presentation	33	34.4			
	Neuropeptide Y (pg/mL)		96		634.43	672.84	78.55
	Ghrelin (pg/mL)		96		275.81	207.51	257.66
	Orexin A (pg/mL)		96		1431.21	1456.37	68.67
	Orexin B (pg/mL)		96		6.49	6.63	0.734
	CBCL depressive problems		96		58.53	56.0	7.46
	CBCL anxiety problems		96		58.66	54.0	8.83
	CBCL somatic problems		96		53.89	50.0	6.96
	CBCL attention problems		96		60.32	60.0	9.23
	CBCL oppositional defiant problems		96		57.64	55.0	8.05
	CBCL conduct problems		96		56.59	52.0	7.62

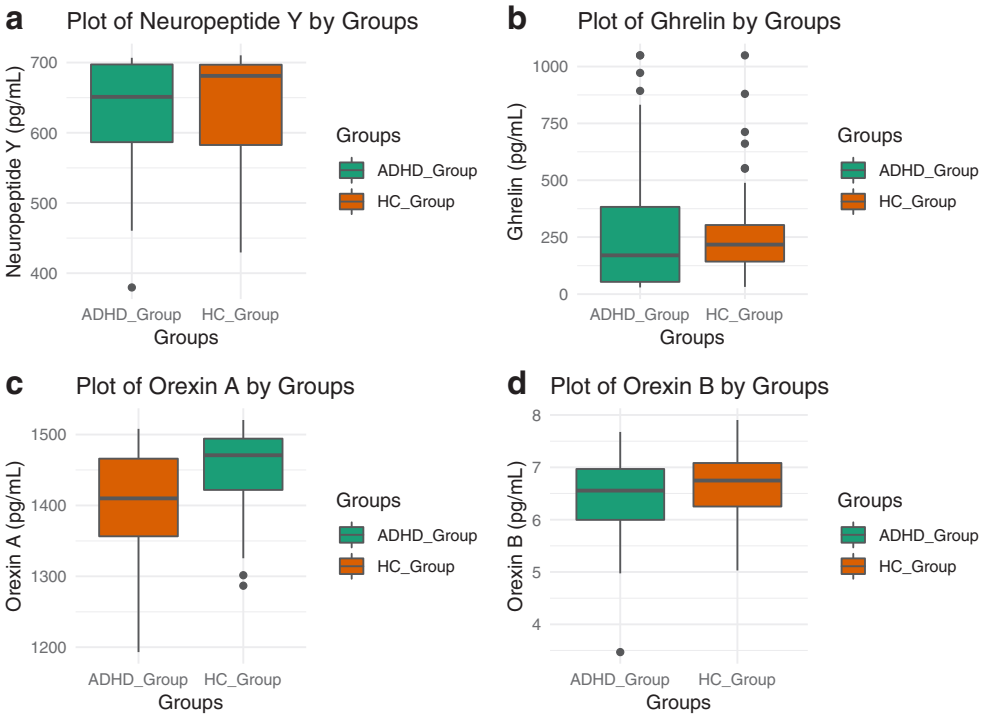

Fig. 3 Box plot of serum **a** neuropeptide Y, **b** ghrelin, **c** orexin A, and **d** orexin B between ADHD and HC groups. ADHD attention deficit and hyperactivity disorder, HC healthy control

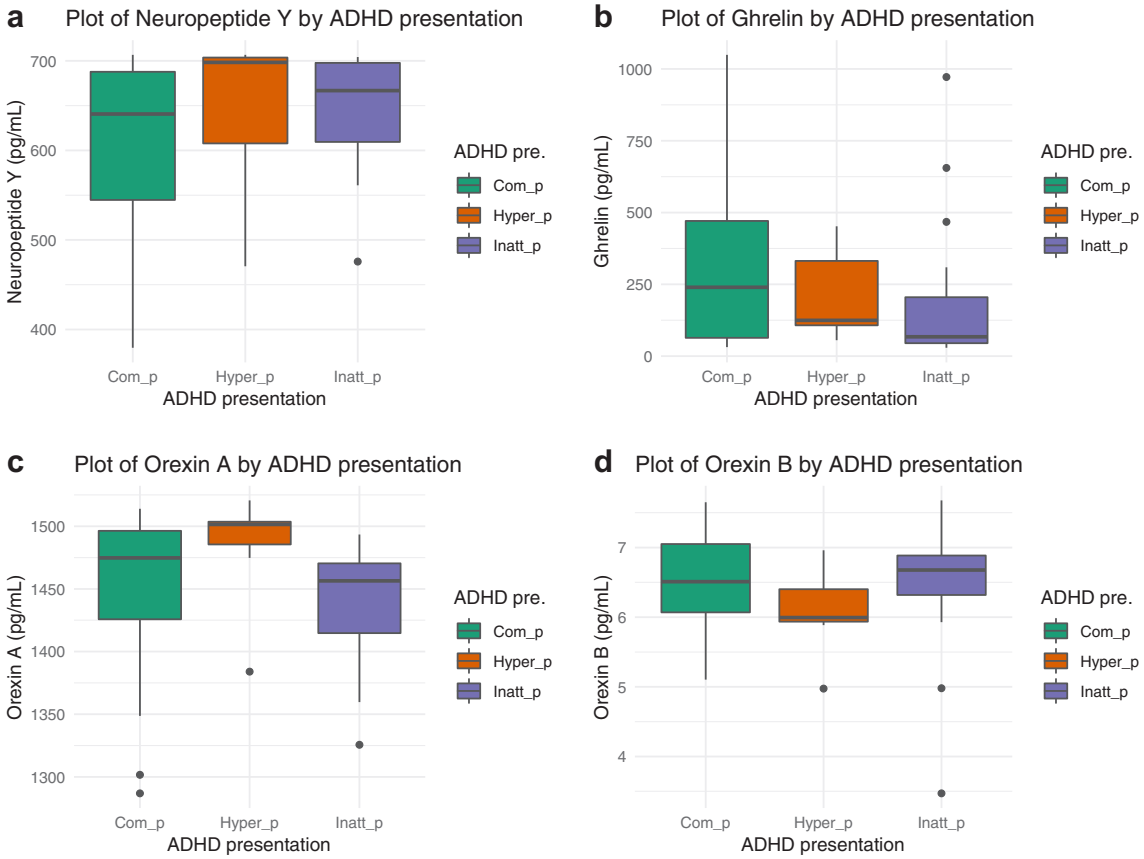

Fig. 4 Box plot of serum **a** neuropeptide Y, **b** ghrelin, **c** orexin A, and **d** orexin B between ADHD presentations groups. ADHD attention deficit and hyperactivity disorder, Com_S combined presentation, Hyper_S hyperactive presentation, Inatt_S inattentive presentation

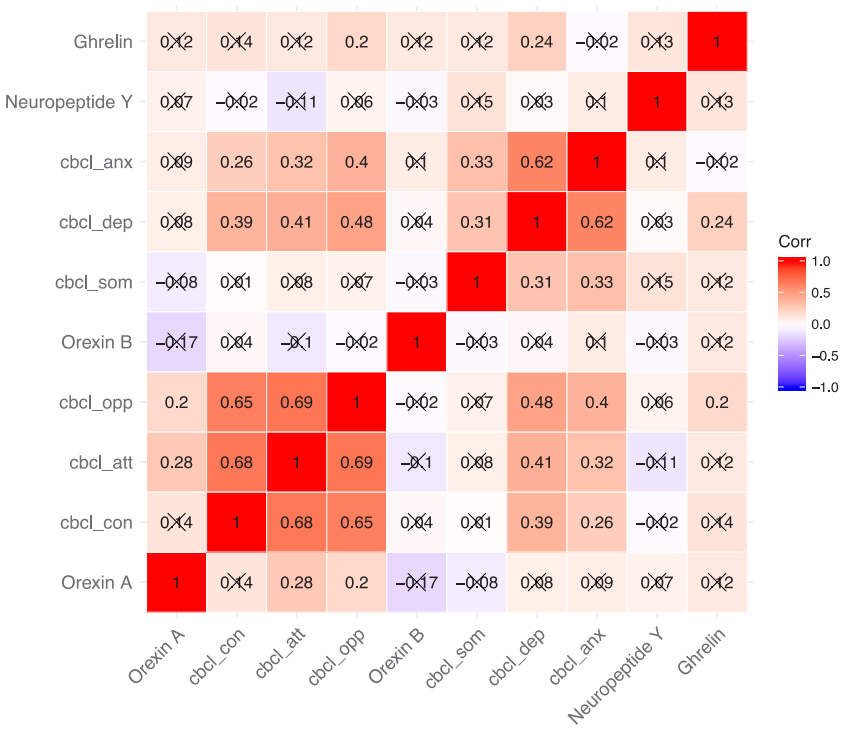

Fig. 5 Correlation map between serum of neuropeptide Y, ghrelin, orexin A, orexin B, and CBCL depressive problems (cbcl_dep), CBCL anxiety problems (cbcl_anx), CBCL somatic problems (cbcl_som), CBCL attention problems (cbcl_att), CBCL oppositional defiant problems (cbcl_opp), and CBCL conduct problems (cbcl_con). CBCL the child behavior checklist

cholinergic basal forebrain, dopaminergic ventral tegmental area, serotonergic raphe nucleus, and many other brain regions have been reported [6, 10]. We found that drug-naive children with ADHD had significantly lower serum orexin A levels compared with the control group. Furthermore, the serum orexin A level was significantly lower in the attention deficit dominant subgroup. Additionally, there were no significant differences between groups in terms of serum levels of neuropeptide Y and ghrelin. Our results indicated that orexin A might be a neurobiological etiological factor in the development of ADHD, particularly symptoms associated with attention. Furthermore, this result could lead to alternative treatment options in the management of ADHD.

Neuropeptide Y is a polypeptide that acts as a co-transmitter, neurohormone, and neuromodulator [37]. Neuropeptide Y was reported to be associated with several psychiatric disorders [38–40]. Abnormal functionality of neuropeptide Y has been reported to be associated with disturbed stress management in anxiety and depressive disorders [41]. There have been limited numbers of studies which investigated neuropeptide Y in ADHD. Serum levels of neuropeptide Y have been reported either increased [42] and similar [43, 44] in children with ADHD compared with healthy subjects. In our study, there was not any significant difference between groups in terms of serum neuropeptide Y level and our finding supported the literature who reported similar serum

Table 2 Comparison of serum neuropeptide Y, ghrelin, orexin A, and orexin B between ADHD and HC groups. ADHD: attention deficit and hyperactivity disorder, HC: healthy control

Serum	Groups	Number	Mean rank	Sum of ranks	Mann–Whitney *U*	*p* value
Neuropeptide Y (pg/mL)	ADHD group	56	46.73	2617.00	1021.000	
	HC group	40	50.98	2039.00		.462
Ghrelin (pg/mL)	ADHD group	56	46.12	2582.50	986.500	
	HC group	40	51.84	2073.50		.321
Orexin A (pg/mL)	ADHD group	56	56.93	1468.00	648.000	
	HC group	40	36.70	3188.00		.000
Orexin B (pg/mL)	ADHD group	56	45.57	2552.00	956.000	
	HC group	40	52.60	2104.00		.223

$p < 0.05$

Table 3 Comparison of serum neuropeptide Y, ghrelin, orexin A, and orexin B levels between ADHD presentations groups. ADHD: attention deficit and hyperactivity disorder

Serum	ADHD presentation	Number	Mean rank	χ^2	p value
Neuropeptide Y (pg/mL)	Inattentive presentation	16	31.06	2.003	
	Hyperactive presentation	7	34.21		.367
	Combined presentation	33	26.05		
Ghrelin (pg/mL)	Inattentive presentation	16	22.00	3.607	
	Hyperactive presentation	7	29.86		.165
	Combined presentation	33	31.36		
Orexin A (pg/mL)	Inattentive presentation	16	21.38	7.292	
	Hyperactive presentation	7	41.07		.026
	Combined presentation	33	29.29		
Orexin B (pg/mL)	Inattentive presentation	16	30.19	2.971	
	Hyperactive presentation	7	18.57		.226
	Combined presentation	33	29.79		

$p < 0.05$

neuropeptide Y levels between children with and without ADHD [43, 44].

Ghrelin acts an important role in higher brain activities such as memory, attention, arousal, and neurogenesis [45]. Also, it has been reported to be associated with inhibiting apoptosis in hypothalamic and cortical neurons. There have been studies which investigated serum ghrelin levels in patients with ADHD for assessing the associations between treatment, appetite, and ghrelin [46–48]. However, there is not any study for investigating the possible role of ghrelin in the etiology of ADHD. In our study, we found similar serum levels of ghrelin between ADHD and healthy control groups. Further studies are needed to clarify the role of ghrelin in the biological etiology of ADHD.

Strengths of our study are as follows: the present study is the first to demonstrate decreased orexin A levels in drug naive patients with ADHD. Second, our results will lead to the investigation of orexigenic peptides in ADHD in additional studies and thus provide another factor to consider in the biological etiology of ADHD. Third, our results provide an opinion in terms of an alternative treatment options for ADHD. Our study also has some limitations. The precise levels of orexin, neuropeptide Y, and ghrelin in the central nervous system can be determined in cerebrospinal fluid; however, lumber puncture is a highly invasive method for both patients and healthy subjects, and this method would cause serious ethical problems. This is the major limitation of the present study. Sex, age, and BMI may affect the serum levels of orexin, neuropeptide Y, and ghrelin; however, our groups were similar in terms of age and sex, and additionally, none of the participants were obese (BMI > 25). However, this issue could also be regarded as a limitation.

In conclusion, the present study is the first to demonstrate the role of serum orexin A levels in drug-naive children with ADHD. Further studies are needed to confirm our results and to show the effects of treatments involving orexin A in patients with ADHD.

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Compliance with ethical standards

The present study was approved by the Namık Kemal University Non-Invasive Clinic Research Ethical Committee.

Conflict of interest The authors declare that they have no conflict of interest.

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