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REGULAR RESEARCH ARTICLE

Role of Appetite Hormone Dysregulation in Symptomology and Executive Function in Adolescents With Attention Deficit Hyperactivity Disorder

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Abstract

Background: Evidence suggests an association of insulin and leptin with attention and executive function. The roles of dysregulated appetite hormones, including insulin and leptin, in the pathomechanisms of attention deficit hyperactivity disorder (ADHD) and associated cognitive function impairment remain unknown.
Methods: In total, 50 adolescents with ADHD were enrolled and age and sex matched with 50 typically developing controls. The parent-reported Swanson, Nolan, and Pelham IV scale and self-reported Barratt Impulsiveness Scale were employed for symptom assessment. The fasting serum concentrations of appetite hormones—leptin, ghrelin, insulin, and adiponectin—were measured. The Wisconsin Card Sorting Test was used to examine executive function.
Results: Generalized linear models with adjustment for age, sex, body mass index, and medications indicated that the adolescents with ADHD had higher levels of insulin ($P = .039$) and leptin ($P = .006$) than did those in the control group. Self-reported attention and self-control symptoms were negatively associated with insulin level ($P = .025$ and .018, respectively) and positively associated with leptin level (both $P < .001$). In addition, insulin level was positively associated with executive function ($P = .031$).
Conclusion: Appetite hormone dysregulation was associated with the symptomology and executive function among adolescents with ADHD. Our results may inspire researchers to further examine the role of appetite hormone dysregulation in ADHD pathogenesis.

Keywords: Metabolic regulation, attention, cognition, teens

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder; it typically emerges during childhood or early adolescence and manifests as age-inappropriate levels of inattention, hyperactivity, and impulsivity that interfere with normal functioning (Franke et al., 2018; Sayal et al., 2018). A systematic review indicated that the

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Significance Statement

Adolescents with ADHD may exhibit appetite hormone dysregulation, such as increased insulin and leptin levels, compared with the non-ADHD controls. Our study found that attention and self-control symptoms were negatively related to insulin level and positively associated with leptin level. Additionally, insulin level was positively associated with executive function. Our findings may suggest the important role of appetite hormone dysregulation in ADHD pathogenesis and related cognitive impairment.

community prevalence of ADHD globally ranges between 2% and 7% (Sayal et al., 2018). ADHD is highly heritable but lacks a definite etiology (Franke et al., 2018; Sayal et al., 2018). Multiple genetic (i.e., dopamine transporter genes, and dopamine receptor genes) and environmental factors (i.e., obesity, childhood head injury, and chaotic family) act together to induce a spectrum of neurobiological vulnerability (Franke et al., 2018; Sayal et al., 2018).

Increasing evidence suggests a biological relationship between ADHD and obesity or overweight (Cortese et al., 2016; Nigg et al., 2016). A meta-analysis of studies enrolling 728 136 individuals (48 161 and 679 975 individuals with and without ADHD, respectively) revealed that the pooled prevalence of obesity was approximately 40% higher in the children with ADHD (10.3% vs 7.4%) than in those without ADHD (Cortese et al., 2016). A significant association between ADHD and obesity or overweight highlights the potential role of dysregulated appetite hormones—insulin, leptin, adiponectin, and ghrelin—in the pathophysiology of ADHD (Marwitz et al., 2015; Ozcan et al., 2018). Fanelli et al. assessed the genetic overlap between ADHD and insulin-related phenotypes (i.e., obesity, type 2 diabetes, and fasting plasma insulin) by estimating pairwise global genetic correlations based on data from previous genome-wide association studies and indicated significant genetic correlations of fasting plasma insulin ($r_g = 0.154$, $P = .005$), fasting plasma glucose ($r_g = 0.123$, $P = 6 \times 10^{-4}$), and obesity ($r_g = 0.386$, $P = 7.16 \times 10^{-30}$) with ADHD (Fanelli et al., 2022). They further suggested the crucial role of brain insulinopathy in the ADHD pathomechanisms (Fanelli et al., 2022).

Furthermore, Özcan et al. measured leptin and adiponectin levels in 36 children and adolescents with ADHD and 40 healthy controls and observed lower adiponectin levels in the ADHD group than in the control group (Ozcan et al., 2018). Işeri et al. found nonsignificantly higher leptin levels in children with ADHD (11.84 ± 19.01 ng/mL) compared with controls (5.19 ± 3.14 ng/mL, $P = .312$) (Iseri et al., 2007). A study employing a rat model of diet-induced obesity reported that a 10-week Western-style diet induced insulin insensitivity, as measured using a quantitative insulin sensitivity check index, and impaired episodic memory in addition to pronounced hyperactivity and impulsivity in adolescent male rats (Marwitz et al., 2015). However, evidence on the association between ADHD and appetite hormone dysregulation remains inconclusive. Additionally, whether appetite hormone dysregulation may be related to symptomology and cognitive dysfunction in patients with ADHD remains unknown.

In the current study, we examined the levels of appetite hormones, namely insulin, leptin, adiponectin, and ghrelin, in adolescents with ADHD and non-ADHD adolescent controls. We further considered the associations between appetite hormone levels and ADHD-related symptomology and cognitive dysfunction. We hypothesized (1) that adolescents with ADHD would be more likely to have higher insulin and leptin levels than would the control group, and (2) that appetite hormone dysregulation would be associated with ADHD symptoms and cognitive deficits.

METHODS

Participants

Adolescents were aged between 12 and 17 years diagnosed with ADHD given by a board-certified child and adolescent psychiatrist based on a comprehensive diagnostic interview involving the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Chinese version (Gau et al., 2005). Age- and sex-matched, typically developing healthy controls were recruited as the comparison group. Those who had other psychiatric disorders, including autism spectrum disorder, schizophrenia, bipolar disorder, major depressive disorder, intellectual disability, and alcohol and substance use disorders, or severe physical disorders, such as congenital anomalies, epilepsy, cerebrovascular diseases, and autoimmune diseases, were excluded from our study sample. In addition, adolescents with hypertension, dyslipidemia, diabetes mellitus, and obesity were also excluded in the current study. Parent-reported Swanson, Nolan, and Pelham IV (SNAP-IV) scale and self-reported Barratt Impulsiveness Scale (BIS) were assessed (Patton et al., 1995; Gau et al., 2008). SNAP-IV is divided into 3 subscales: inattention, hyperactivity, and oppositional subscale (Gau et al., 2008). BIS includes 30 items scored to yield 6 first-order factors, including attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness (Patton et al., 1995). This study was approved by the Institutional Review Board of Taiwan Veterans General Hospital and the Department of Health of Taiwan. Written informed consent was obtained from the participants and their parents.

Measurement of Appetite Hormones

Fasting serum samples were collected between 9 AM and 12 PM in serum separator tubes, clotted for 30 minutes, and stored at –80°C until use. Each participant was confirmed with no food intake after midnight. The appetite hormones, including leptin, ghrelin, insulin, adiponectin, were examined. Ghrelin was measured using a radioimmunoassay kit (Peninsula Laboratories, Inc., San Carlos, CA, USA), and insulin concentrations were also analyzed using a radioimmunoassay kit (Coat-A Count Insulin, Diagnostic Product Corporation, Los Angeles, CA, USA). Serum adiponectin level was measured using a quantitative Human Adiponectin ELISA Kit (B-Bridge International, Inc., Mountain View, CA, USA). All assays were performed according to the vendor's instructions. The final absorbance of each sample of the mixture was measured and analyzed at 450 nm using an ELISA plate reader with Bio-Tek Power Wave Xs and Bio-Tek's KC junior software (Winooski, VT, USA). The standard range was

considered as specified in the vendor's instructions. A linear regression R-square value of at least 0.95 was considered a reliable standard curve.

Assessment of Cognitive Function

In the current study, the Wisconsin Card Sorting Test (WCST) was examined for executive function. WCST required strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behavior towards achieving a goal, and modulating impulsive responding. In addition, to minimize the type 1 error from multiple comparison correction, we followed the a priori findings of our previous study that a certain subset of WCST, including percentage perseverative errors, percentage conceptual level responses, categories completed, and trials to complete first category, was more likely to be significant for the relationship with appetite hormones (Tu et al., 2017; Chen et al., 2020). We focused on these WCST subset results for the correlation analyses with appetite hormones in current study (Tu et al., 2017; Chen et al., 2020).

Statistical Analysis

For between-group comparisons, the F-test was used for continuous variables, and Pearson's χ^2 test was used for categorical variables. Generalized linear models (GLMs) with the adjustment of age, sex, body mass index (BMI), and medications (methylphenidate or atomoxetine) were used to compare levels of appetite hormones between groups. GLMs with the adjustment of group, age, sex, BMI, and medications (methylphenidate or atomoxetine) were performed to examine the association between appetite hormones and clinical symptoms, including SNAP-IV and BIS scores. GLMs with additional adjustment of clinical symptoms (SNAP-IV and BIS scores) were used for assess the association between appetite hormones and executive function. Two-tailed $P < .05$ was considered statistically significant. All data processing and statistical analyses were performed using the SPSS version 17 software (SPSS Inc.).

RESULTS

In all, 50 adolescents with ADHD and age-/sex-matched controls were included in current study, with an average age of approximately 13 years and male predominance (Table 1). The ADHD cohort had higher total SNAP-IV ($P < .001$) and BIS ($P < .001$) scores than the control group (Table 1). Scores in inattention ($P < .001$), hyperactivity ($P < .001$), and oppositional ($P < .001$) subscales of SNAP-IV and in attention ($P < .001$), motor ($P = .020$), self-control ($P = .002$), and cognitive complexity ($P = .003$) subscales of BIS differed significantly between groups (Table 1). BMI did not differ between groups ($P = .786$) (Table 1). In addition, adolescents with ADHD were more likely to have higher levels ($P = .014$) of leptin and insulin ($P = .018$) than did the controls (Table 1). The difference in leptin ($P = .006$) and insulin ($P = .039$) levels between groups remained significant with adjustment for age, sex, BMI, and medications (Figure 1).

GLMs with the adjustment for group, age, sex, BMI and medications found a negative association between insulin level and attention ($P = .025$) and self-control ($P = .018$) subscale scores of BIS and a positive association between leptin level and attention ($P < .001$), motor ($P < .001$), self-control ($P < .001$), and cognitive instability ($P = .001$) subscale scores of BIS (Table 2). GLM with additional adjustment of clinical symptoms showed a positive relationship between insulin level and executive function ($P = .031$) (Table 3).

DISCUSSION

Our findings support the study hypothesis that adolescents with ADHD are more likely to have higher insulin and leptin levels than non-ADHD controls. Clinical symptoms, especially greater inattention and poorer self-control as indicated by BIS score, were negatively associated with insulin level and positively associated with leptin level after adjustment for age, sex, BMI, and medications. Furthermore, insulin level was positively associated with executive function, as measured using the WCST, with additional adjustment for clinical symptoms.

The role of appetite hormone dysregulation in the pathophysiology and symptomology of ADHD has rarely been investigated. As mentioned, a growing body of evidence indicates a prominent association between ADHD and obesity, which is associated with higher fasting insulin and leptin levels and insulin resistance (Zimmet et al., 1996; Antunes et al., 2009; Zuo et al., 2013; Ling et al., 2016). Ling et al. observed a higher fasting insulin level and greater Homeostatic Model Assessment for Insulin Resistance index values in adolescents with obesity (BMI > 85th percentile) than in controls (Ling et al., 2016). Antunes et al. reported a significant association of increased leptin level with greater BMI in a cohort of adolescents with an average BMI of 26.8 ± 4.4 kg/m^2 (Antunes et al., 2009). In the present study, we excluded individuals with obesity and adjusted for BMI and medications; nevertheless, we found that adolescents with ADHD had higher insulin and leptin concentrations than did non-ADHD controls, suggesting that appetite hormone dysregulation has an independent role in ADHD pathogenesis. Furthermore, our results suggest that appetite hormone dysregulation may be a shared factor in ADHD and obesity (Zimmet et al., 1996; Antunes et al., 2009; Zuo et al., 2013; Ling et al., 2016) and may indicate that ADHD in childhood or adolescence is an independent risk factor for developing obesity in adulthood (Pinhas-Hamiel et al., 2021).

A negative and positive association of insulin and leptin levels, respectively, with symptom severity (attention and self-control) and a positive association between insulin level and executive function may indicate a complicated compensatory process of insulin and leptin regulation in patients with ADHD. A 34-year follow-up study of 1212 nondiabetic participants reported a U-shaped association between fasting insulin and cognitive functioning (Mehlig et al., 2018). Leptin is thought to regulate neuronal excitability and synaptic plasticity in the hippocampus, and insulin was reported to be involved in neuroprotection, cognition, memory potentiation, synaptic plasticity, selective attention, and anti-inflammation (Erichsen et al., 2022). Therefore, leptin resistance and insulin resistance, which lead to increased production of leptin by adipocytes and insulin by β-cells, may affect various physiological processes, including food intake, inflammation, and cognition (Geroldi et al., 2005; Forny-Germano et al., 2018; Erichsen et al., 2022). Evidence suggests that leptin resistance and insulin resistance are related to impaired attention, memory, and hippocampal long-term potentiation, which may further stimulate attention and self-control symptoms and executive dysfunction in patients with ADHD (Erichsen et al., 2022). The above paradoxical phenomenon may imply that the dysregulated

Table 1. Demographic Characteristics, Clinical Symptoms, and Levels of Appetite Hormones in Adolescents with ADHD

	Adolescents with ADHD (n = 50)	Controls (n = 50)	P-value
Age (y, SD)	13.60 (1.55)	13.98 (1.33)	.192
Sex (n, %)			.254
Male	40 (80.0)	34 (68.0)	
Female	10 (20.0)	16 (32.0)	
BMI (SD)	20.78 (3.96)	20.56 (3.46)	.768
SNAP-IV total scores (SD)	36.08 (16.51)	12.52 (9.15)	<.001
Inattention subscale scores	15.52 (6.11)	5.84 (4.05)	<.001
Hyperactivity subscale scores	9.46 (6.49)	1.72 (2.26)	<.001
Oppositional subscale scores	11.10 (6.51)	4.96 (4.54)	<.001
BIS total scores (SD)	70.6 (11.69)	62.20 (6.06)	<.001
Attention subscale scores	12.40 (3.19)	1012 (2.24)	<.001
Motor subscale scores	15.88 (3.34)	14.52 (2.35)	.020
Self-control subscale scores	15.56 (3.59)	13.52 (2.74)	.002
Cognitive complexity subscale scores	12.92 (2.67)	11.34 (2.42)	.003
Perseverance subscale scores	7.28 (1.60)	6.90 (1.42)	.212
Cognitive instability subscale scores	6.32 (2.20)	5.80 (1.59)	.179
ADHD medication treatment (n, %)			
Methylphenidate	18 (36.0)		
Atomoxetine	12 (24.0)		
Appetite hormones			
Leptin (ng/L)	26192.83 (52720.84)	7330.37 (9380.45)	.014
Adiponectin (ug/L)	7681.22 (4512.95)	6283.34 (3438.47)	.085
Ghrelin (fmol/mL)	75.93 (89.93)	62.93 (71.83)	.427
Insulin (mU/L)	32.85 (37.09)	18.70 (19.01)	.018
WCST (SD)			
% Perseverative errors	11.34 (5.84)	11.36 (9.52)	.990
% Conceptual level responses	72.74 (13.45)	74.82 (15.64)	.478
Categories completed	5.60 (0.95)	5.74 (0.94)	.461
Trials to complete first category	15.22 (10.35)	12.48 (3.86)	0.082

Abbreviations: ADHD, attention deficit hyperactivity disorder; BIS, Barratt Impulsiveness Scale; BMI, body mass index; SNAP-IV, Swanson, Nolan, and Pelham Rating Scale-IV; WCST, Wisconsin Card Sorting Test.

homeostasis between appetite hormones (i.e., insulin and leptin), but not a single appetite hormone dysregulation, played the crucial role in the ADHD symptomology and associated cognitive function impairment.

This study has several limitations. First, only the WCST was used for measuring cognitive function. Additional studies may be required to comprehensively evaluate the cognitive function of adolescents with ADHD. Second, ADHD medication was not discontinued during cytokine examination and cognitive assessment. Allowing patients to continue their medications was ethically appropriate and prevented symptom exacerbation during the study. Furthermore, this approach yielded more naturalistic data. However, a drug-free study design would be required to validate our findings. Third, following corrections for multiple comparisons, the *P* value decreased from .05 to .05/4 (.0125) in Table 3. The association between insulin level and executive function became nonsignificant ($P > .0125$), which indicated that insulin may not directly play a crucial role in executive function deficits. Further studies may be necessary to validate our results. Finally, the criteria of ADHD in the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Chinese version, are based on the DSM, fourth edition (Gau et al., 2005). Further studies would be required to assess whether our results may be generalized to those who were diagnosed with ADHD based on the DSM-5.

In conclusion, adolescents with ADHD were more likely to have higher insulin and leptin levels than were those without ADHD after adjustment for BMI and medications. ADHD symptomology, measured using the BIS, was negatively associated with insulin level and positively associated with leptin level. Insulin level was further independently associated with executive function, although the statistical significance disappeared after the corrections for multiple comparisons. Our results may inspire researchers to further examine the role of appetite hormone dysregulation in ADHD pathogenesis.

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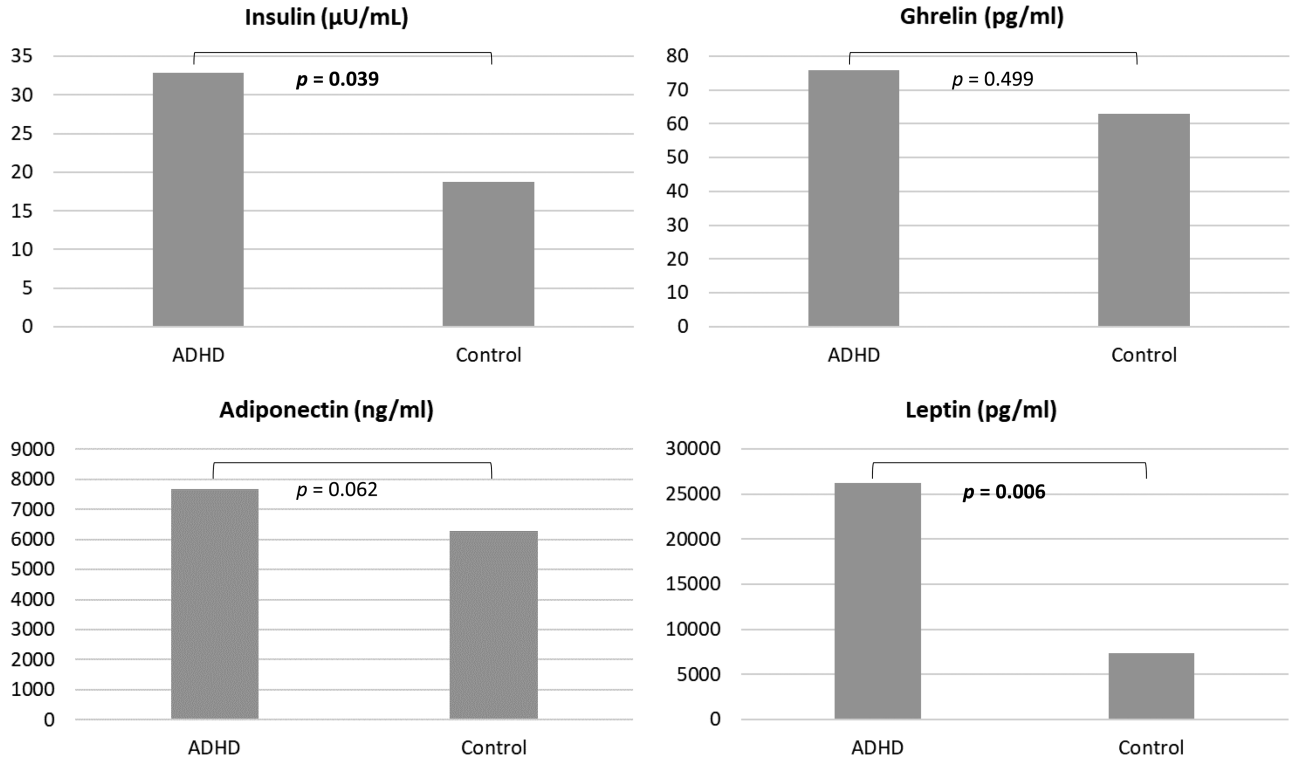

Figure 1. Estimated marginal means of appetite hormones between groups with adjustment of age, sex, body mass index (BMI), and medications. ADHD, attention deficit hyperactivity disorder.

Table 2. GLMs With Adjustment of Group, Age, Sex, BMI, and Medications Between Clinical Symptoms and Levels of Insulin and Leptin

	Insulin			Leptin		
	B	t	P-value	B	t	P-value
SNAP-IV total scores	0.017	0.362	.718	0.000	0.931	.354
Inattention subscale scores	–0.002	–0.134	.894	0.000	0.158	.875
Hyperactivity subscale scores	0.013	0.754	.453	0.000	1.858	.066
Oppositional subscale scores	0.007	0.337	.737	0.000	0.493	.623
BIS total scores	–0.037	–1.196	.235	0.000	5.528	<.001
Attention subscale scores	–0.021	–2.271	.025	0.000	3.799	<.001
Motor subscale scores	0.007	0.742	.460	0.000	4.575	<.001
Self-control subscale scores	–0.025	–2.411	.018	0.000	3.948	<.001
Cognitive complexity subscale scores	–0.002	-0.196	.845	0.000	1.849	.068
Perseverance subscale scores	0.001	0.195	.846	0.000	–0.748	.456
Cognitive instability subscale scores	0.003	0.381	.704	0.000	3.475	.001

Bold values indicate the statistical significance ($P < 0.05$). Abbreviations: BIS, Barratt Impulsiveness Scale; BMI, body mass index; GLM, generalized linear model; SNAP-IV, Swanson, Nolan, and Pelham Rating Scale-IV.

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Contributions

Dr M.H.C., Dr Y.M.B., Dr J.W.H. designed the study, wrote the protocol, and drafted the manuscript. Dr M.H.C. performed the statistical analyses. Dr K.L.H. and Dr S.J.T. reviewed the draft and revision and assisted with the preparation and proofreading of the manuscript.

Table 3. GLMs With Adjustment of Group, Age, Sex, BMI, Clinical Symptoms, and Medications between Executive Function and Levels of Insulin and Leptin

Cognitive function parameters	Insulin			Leptin		
	B	t	*P*-value	B	t	*P*-value
WCST (SD)						
% Perseverative errors	−0.038	−1.337	.185	0.000	−1.522	.132
% Conceptual level responses	0.079	1.504	.136	0.000	0.441	.660
Categories completed	0.007	2.185	.031	0.000	0.471	.639
Trials to complete first category	−0.006	−0.230	.818	0.000	−0.042	.967

Bold values indicate the statistical significance ($P < 0.05$). Abbreviations: BMI, body mass index; GLM, generalized linear model; WCST, Wisconsin Card Sorting Test.

Interest Statement

All authors have no financial relationships relevant to this article to disclose. All authors declared no conflicts of interest.

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