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ORIGINAL PAPER

Effects of Methylphenidate and Bupropion on DHEA-S and Cortisol Plasma Levels in Attention-deficit Hyperactivity Disorder

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Abstract We evaluated plasma levels of DHEA-S and cortisol before and after treating ADHD patients with one of two medications: methylphenidate (n = 12) or bupropion (n = 10). Boys with ADHD (combined type) were evaluated with the Korean ADHD rating scale (K-ARS) and the computerized ADHD diagnostic system (ADS). All assessments were measured at baseline and repeated after 12 weeks. There were significant clinical improvements in both treatment groups as measured by K-ARS and ADS. DHEA-S levels increased from baseline to endpoint, but cortisol levels did not change significantly. This study suggests that both methylphenidate and bupropion increase plasma levels of DHEA-S in boys with ADHD.

Keywords Attention deficit disorder with hyperactivity · Dehydroepiandrosterone sulfate · Methylphenidate · Bupropion

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders of childhood and adolescence [1]. ADHD is associated with alterations in prefrontal cortex through dopaminergic and noradrenergic neurotransmission [2].

Several studies have employed laboratory analyses to assess the potential differences between control and ADHD groups. Since there are no known specific cognitive, metabolic, or neurological/biological markers for ADHD, uncertainty exists for assessing symptom changes in the disorder [3]. The development of laboratory measures for the assessment of symptom changes in ADHD would be helpful for both understanding and treating the essential underlying pathophysiological processes.

Neuroactive steroids, or neurosteroids, are produced in the brain and are capable of modifying neural activities. Dehydroepiandrosterone (DHEA), a major circulating neurosteroid in

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humans, and its sulfate ester (DHEA-S) are adrenal hormones that are also synthesized *de novo* in the brain. DHEA and DHEA-S have been reported to have multiple effects on the central nervous system (CNS), affecting memory, long-term potentiation, anxiety, and mood [4]. A relationship between ADHD and neurosteroid levels has been suggested by previous studies [5, 6]. DHEA-S is known to increase the catecholamine levels (dopamine and norepinephrine) [7]. Previous papers have reported that clinical symptomatology and plasma levels of DHEA are inversely correlated in ADHD patients. For example, plasma levels of DHEA and DHEA-S were inversely correlated with hyperactivity symptoms in ADHD patients [5].

Significant increases in plasma levels of DHEA and DHEA-S were reported after 3 months of methylphenidate treatment in 15 boys with ADHD, but the precise underlying mechanisms were unclear [6]. Concomitant increases in plasma levels of cortisol were not observed. Since cortisol is an index of adrenal function, these results show that the increase in DHEA and DHEA-S does not result from nonspecific adrenal hyperactivity. The results also indicate that these neurosteroids may play a role in the therapeutic effects of methylphenidate. However, there was also no significant correlation between clinical improvements and the level of DHEA or DHEA-S.

Methylphenidate is the most widely used medication for the treatment of ADHD. It exerts its effects through the dopaminergic [8], serotonergic [9], and noradrenergic systems [10]. However, its effects on other neurophysiological systems, such as the neurosteroidal system, remain unknown [11].

Bupropion is also used frequently in the treatment of ADHD. Bupropion has only weak affinities for the dopamine, serotonin, and norepinephrine transporters [12]. Although bupropion belongs to a different drug class than stimulants, it has a unique pharmacological profile that is somewhat similar to that of stimulants [13]. Both stimulants and bupropion have proven to be more effective than placebo in the management of ADHD symptoms [14].

Both DHEA and its sulfated derivative can be readily assayed. However, DHEA-S is measured more frequently than DHEA because circulating levels of DHEA-S are approximately 500 times higher [15] due to its lower metabolic clearance rate and minimal diurnal variation [16]. In the present study, we used cortisol levels as an index of adrenal function. We evaluated the plasma levels of DHEA-S and cortisol before and after treating ADHD patients with two medications: methylphenidate and bupropion. We hypothesized that if significant changes in DHEA-S levels were present in both treatment groups, the changes in DHEA-S levels could be suggested for the indirect assessment of ADHD symptom changes.

Materials and Methods

Study Population

The study subjects were all outpatients at Guro Hospital, Korea University Medical Center. None had received any medication for at least 2 months prior to the commencement of the study. Only boys with combined-type ADHD and without any comorbidities were included; those with any neurological disorders, conduct disorders, or learning disabilities were excluded. The study was approved by the Institutional Review Board of Guro Hospital, Korea University Medical Center. The care providers of all subjects provided informed-consent forms for the participation of their children in this study.

Patients were randomly assigned to 12 weeks of treatment with either methylphenidate (at a flexible daily dose of 5–20 mg/day) or bupropion (at a flexible daily dose of 150–300 mg). Doses were gradually increased according to clinical responses. No other psychotropic medications were permitted during the study. All clinical and laboratory assessments were repeated at the end of 12 weeks of treatment.

The study population consisted of 22 young male subjects, 12 in the methylphenidate treatment group and 10 in the bupropion treatment group, who were 139.1 ± 35.6 months old (mean ± standard deviation) and 136.4 ± 47.5 months old, respectively.

Clinical Assessment

We assessed intelligence quotient (IQ) with the Korean version of the Wechsler intelligence scale for children.

ADHD symptomatology was assessed using the Korean ADHD rating scale (K-ARS), which is an index based on the DSM-IV that is specifically designed for ADHD. The K-ARS was originally developed from the ADHD Rating Scale-IV [17] and translated into Korean. Its reliability and validity have been established [18]. This scale consists of 18 items originating from DSM-IV ADHD diagnostic criteria. The K-ARS comprises two subscales (inattention and hyperactivity-impulsivity), each of which is scored independently. Each DSM-IV ADHD criterion is rated on the following 4-point Likert scale: 0 = not present; 1 = sometimes present; 2 = often present; 3 = very often present. The maximum possible score for each scale is 27, with the total maximum score being 54.

To diagnose ADHD, the computerized ADHD diagnostic system (ADS) was used. ADS was developed for the assessment of ADHD and to evaluate the effects of treatment. It is commonly used as a diagnostic instrument for ADHD in Korea [19]. ADS is a type of continuous performance test and comprises visual and auditory tasks. In this study, participants performed visual tasks, with the major outcome variables being an omission error (failing to respond to a target), a commission error (responding when there is no target), the response time, and the response variability (standard deviation of response time). The omission and commission errors measure inattention and impulsivity, respectively. ADHD patients tend to exhibit longer response times to a target and increased response variability. ADS test results are commonly expressed as T-scores relative to predetermined average scores for all the major variables. This standardization was performed, and the reliability coefficient of ADS (Cronbach's alpha) was 0.85 [19].

Laboratory Assessment

Procedure

Since neurosteroid levels vary during the day, all peripheral blood testing was performed between 08:00 and 10:00 a.m. Subjects were instructed to abstain from unusual physical activity or stress for a period of 24 hours prior to venous blood sampling.

Measurements of Plasma Cortisol and DHEA-S Levels

Plasma DHEA-S levels were measured by radioimmunoassay using the Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles, CA). The lower limit of detection was

1.1 μg/dl, and the inter- and intra-assay coefficients of variation were 7.7% and 3.8%, respectively. Plasma cortisol levels were also measured by radioimmunoassay using the Coat-A-Count kit, for which the lower limit of detection was 0.2 μg/dl, and the inter- and intra-assay coefficients of variation were 4.0% and 4.7%, respectively.

Statistical Analysis

Baseline demographic and clinical variables were compared between the two groups using Mann–Whitney *U* tests for continuous outcomes. The Wilcoxon signed–rank test with two-tailed probability was used to compare the clinical-psychometric data and levels of DHEA-S and cortisol before and after 12 weeks of each treatment. Pearson's correlation test was then applied to the resulting data. A probability value of $p < 0.05$ was considered statistically significant. All data analyses were performed using SPSS version 10.0.

Results

Baseline Demographic, Psychometric, and Laboratory Variables

None of the assessed variables differed significantly between the two treatment groups (Table 1). All participants were evaluated for adverse events at each visit, which included an interview of their care providers. There were no significant adverse events that required a medication change.

Table 1 Demographic, psychometric, and laboratory variables in the two treatment groups

		Methylphenidate treatment group (n = 12)	Bupropion treatment group (n = 10)	p
Age, months		136.4 ± 47.5	139.1 ± 35.6	N.S.
KEDI-WISC	Total IQ	97.7 ± 24.8	97.3 ± 13.1	N.S.
K-ARS subscale score	Inattention score	15.2 ± 5.0	15.4 ± 4.9	N.S.
	Hyperactivity-impulsivity score	11.6 ± 7.0	11.60 ± 7.3	N.S.
	Total score	26.8 ± 10.7	27.0 ± 11.5	N.S.
ADS T-score	Omission error	94.4 ± 61.3	66.0 ± 15.6	N.S.
	Commission error	73.3 ± 31.2	78.6 ± 36.4	N.S.
	Response time	54.7 ± 25.7	57.4 ± 17.7	N.S.
	Response variability	90.2 ± 37.3	88.7 ± 28.1	N.S.
Baseline steroid level (μg/dl)	DHEA-S	88.1 ± 73.9	72.9 ± 85.0	N.S.
	Cortisol	7.7 ± 2.0	11.5 ± 6.0	N.S.

Data are mean ± standard deviation values

Mann-Whitney *U* tests. N.S.: not significant

KEDI-WISC, Korean version of the Wechsler intelligence scale for children; K-ARS, Korean ADHD rating scale; ADS, computerized ADHD diagnostic system; DHEA-S, dehydroepiandrosterone-sulfate ester

Baseline IQ scores, K-ARS, ADS T-scores, and neurosteroid levels in the two treatment groups are presented in Table 1. None of these measures differed significantly between the two groups.

Changes in Scores Between Baseline and Posttreatment Assessments

Baseline and posttreatment assessments of K-ARS, ADS T-scores, and neurosteroid levels were compared using the Wilcoxon signed-rank test. Plasma levels of DHEA-S increased significantly from 81.2 ± 77.6 to 97.3 ± 92.3 μg/dl, but there was no significant change in cortisol levels (Fig. 1). When we analyzed DHEA-S and cortisol levels for each treatment group separately, both groups again showed significant increases of DHEA-S plasma levels but non-significant changes of cortisol plasma levels (Methylphenidate treatment group: DHEA-S levels from 88.1 ± 73.9 to 105.3 ± 85.1, $p = 0.032$, cortisol levels from 7.7 ± 2.0 to 9.0 ± 4.3, $p = 0.345$ / Bupropion treatment group: DHEA-S levels from 72.9 ± 85.0 to 87.8 ± 104.1, $p = 0.048$, cortisol levels from 11.47 ± 6.0 to 12.44 ± 6.0, $p = 0.579$).

All K-ARS scores showed significant changes, and the commission error and response variability in ADS outcome-variable T-scores showed significant decreases (Fig. 1).

The size of changes in K-ARS, ADS T-scores, and neurosteroids were compared between the two treatment groups using independent sample *t*-tests (Table 2). The significant decreases in the hyperactivity-impulsivity scores of K-ARS were greater in the methylphenidate treatment group than in the bupropion treatment group. However, the other comparisons revealed no other significant differences.

Correlation of Baseline Levels and Changes in DHEA-S with other Assessment Variables

No correlation was found among the baseline values of DHEA-S plasma levels, K-ARS, and ADS subscale scores. There was also no correlation between DHEA-S plasma levels and changes in K-ARS and ADS subscale scores.

Discussion

Both methylphenidate and bupropion treatments significantly increased DHEA-S plasma levels in this study. These increases were not accompanied by increases in cortisol levels, which suggests that the increase in neurosteroids resulted from a specific process rather than nonspecific adrenal hyperactivity.

DHEA and DHEA-S modulate many neurobiological functions at two major CNS receptors: the gamma-aminobutyric acid (GABA) receptor and the N-methyl-D-aspartate (NMDA) receptor [20]. DHEA and DHEA-S mainly affect the $GABA_A$ receptor [21]. DHEA-S has been shown to act in vitro as a negative noncompetitive modulator of the $GABA_A$ receptor complex [22]. ADHD is related to altered functions of the prefrontal cortex and its connection to the striatum and cerebellum. Adequate levels of dopamine are required for prefrontal-cortex control of behavior and attention [2]. Maayan et al. suggests that the antagonistic activity of DHEA and DHEA-S at the $GABA_A$ receptor complex plays a critical role in the diminution of ADHD symptoms because striatal dopaminergic neurotransmission is regulated by GABA-ergic input [6]. Another mechanism underlying the

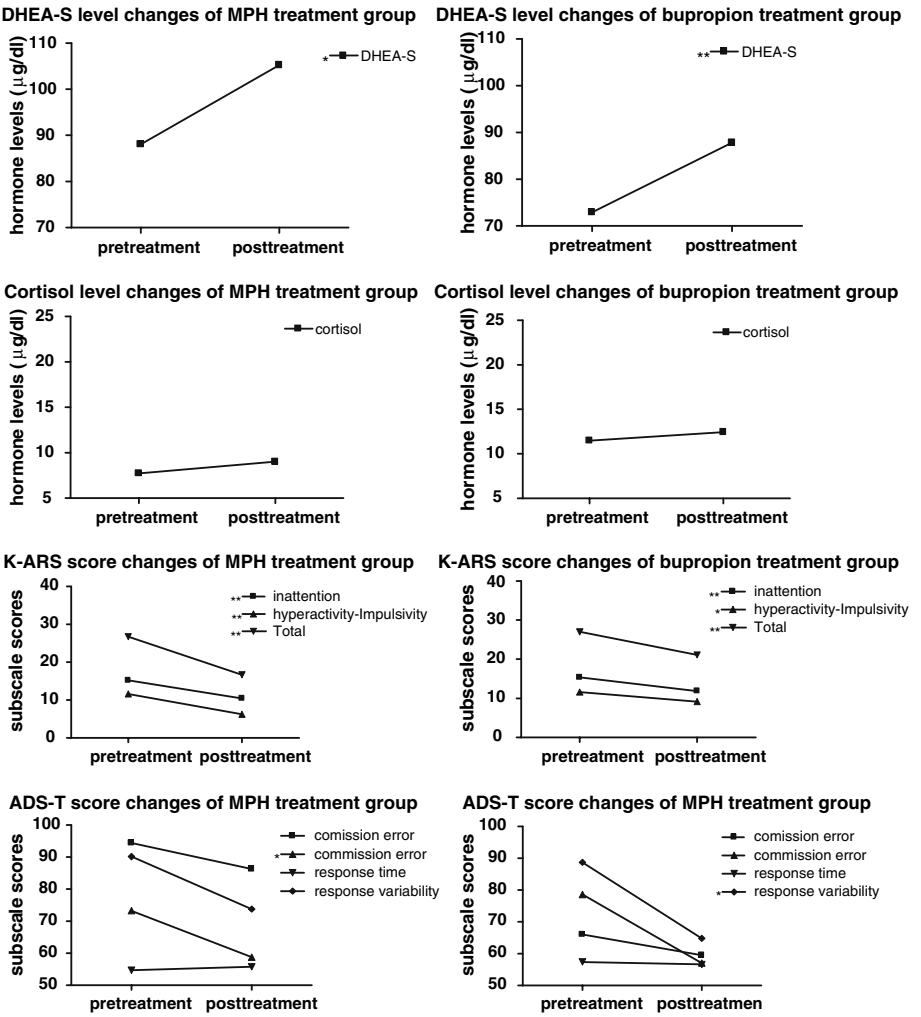

Fig. 1 Comparison of pre- and post-treatment measurements in attention-deficit hyperactivity disorder. Wilcoxon signed-rank test. $^{*}p < 0.05$, $^{**}p < 0.01$, ADHD, Attention-deficit hyperactivity disorder; DHEA-S, Dehydroepiandrosterone-sulfate ester; K-ARS, Korean ADHD rating scale; ADS-T, Computerized ADHD diagnostic system T-score

effects of DHEA and DHEA-S may be NMDA- or glutamate-enhanced neurotransmission via sigma receptors [23]. Impaired NMDA receptor function in the prefrontal cortex of spontaneously hyperactive rats has been suggested to be related to impaired cognition and an inability to sustain attention [24]. DHEA enhances the neuronal response to NMDA by acting at the NMDA receptor [23]; this may be also linked to the diminution of ADHD symptoms.

Both methylphenidate and bupropion showed therapeutic effects, with all K-ARS subscales decreasing significantly. However, the hyperactivity-impulsivity score of K-ARS decreased significantly more in the methylphenidate treatment group, which is consistent with a previous report that showed that bupropion had lower efficacy [14].

Table 2 Comparison of changes in K-ARS, ADS T-scores, and levels of neurosteroids between the two treatment groups

	Variable	Methylphenidate group	Bupropion group	*p*
K-ARS subscale score changes	Inattention score	–4.75 ± 4.4	–3.50 ± 1.1	N.S.
	Hyperactivity-impulsivity score	–5.33 ± 3.4	–2.40 ± 2.9	0.043
	Total score	–10.08 ± 6.6	–5.90 ± 3.7	N.S.
ADS T-score changes	Omission error	–8.17 ± 90.3	–6.50 ± 18.7	N.S.
	Commission error	–14.50 ± 25.2	–21.60 ± 34.7	N.S.
	Response time	1.08 ± 25.6	–0.80 ± 14.7	N.S.
	Response variability	–16.42 ± 33.8	–23.90 ± 26.6	N.S.
Steroid level changes (μg/dl)	DHEA-S	17.17 ± 24.2	14.90 ± 20.7	N.S.
	Cortisol	1.28 ± 4.5	0.97 ± 5.3	N.S.

Data are mean ± standard deviation values

Mann–Whitney *U* tests. N.S.: not significant

Although the hyperactivity-impulsivity score of K-ARS showed a significant difference, there was no significant difference in the amount of change in DHEA-S levels between both treatment groups. Baseline levels of DHEA-S and subsequent changes were not correlated with other assessment variables for ADHD in this study. There can be at least two possible explanations for these results. One possibility is that the neural process that caused the changes in DHEA-S plasma levels is not directly related to the pathophysiologic processes that underlie ADHD and that DHEA-S does not specifically reflect the pathophysiologic changes of ADHD. A second possibility is that plasma levels of DHEA and DHEA-S need to reach a certain threshold before the severity of ADHD symptoms is attenuated, thereby showing a possible but still unproven neurosteroid protective effect. If the minimum required levels of DHEA and DHEA-S levels are not reached, the protective effect of the neurosteroids may be nullified, resulting in the development of prominent ADHD symptoms.

This study had some limitations. Among the major limitations of this study are the lack of a control group and the small sample size. In the absence of a control group, no direct causal relationship between observed clinical improvements and DHEA-S level changes can be inferred. However, it could be demonstrated that levels of DHEA-S change when clinical symptoms improve with pharmacologic treatment of ADHD.

Rather than directly measure brain levels of DHEA-S, this study investigated peripheral plasma levels of DHEA-S level rather than directly measuring the brain levels. However, the previously reported linear relationship between plasma and cerebrospinal concentrations of DHEA and DHEA-S indicates that plasma levels of both neurosteroids reflect CNS levels [25].

Future studies that include more patients, females, and a psychiatric control group should further assess the relationship between DHEA levels and clinical symptoms in ADHD patients.

Summary

Both methylphenidate and bupropion showed therapeutic effects in Korean boys with ADHD; all K-ARS subscales decreased significantly. The hyperactivity-impulsivity score

of K-ARS decreased significantly more in the methylphenidate treatment group, which is consistent with a previous report that stated bupropion had lower efficacy. Because we did not have a control group, no causal relationship between observed clinical improvements and DHEA-S level changes can be inferred. However, the current study showed that both methylphenidate and bupropion increase plasma levels of DHEA-S.

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