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Relationship between the SNAP-25 gene and the effects of methylphenidate on the anterior cingulate cortex of patients with adult attention deficit hyperactivity disorder: a magnetic resonance spectroscopy study

G.A. ÜNAL[1], A.N. İNCI KENAR[2], E. TEPELI[3], Y. KIROĞLU[4], H. HERKEN[2]

[1]Psychiatry Clinic, Kozan State Hospital, Adana, Turkey
[2]Department of Psychiatry, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[3]Department of Medical Genetics, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[4]Department of Radiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey

Abstract. – OBJECTIVE: The effects of certain genetic alterations in the brain function of patients with attention deficit hyperactivity disorder (ADHD) remain unclear and, in fact, there is a limited amount of data in this field. For example, the relationship between the SNAP-25 polymorphism and brain metabolites in response to methylphenidate (MPH) has yet to be investigated. Thus, the present study aimed to determine the relationship between changes in creatine (Cr), choline (Cho), and N-acetyl aspartate (NAA) levels in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) of adults with ADHD and the SNAP-25 gene polymorphism following the use of MPH.

PATIENTS AND METHODS: The present study assessed 60 patients between 18 and 60 years of age who were diagnosed with ADHD according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Genetic analyses were carried out using blood samples obtained from the ADHD patients and included a detailed clinical evaluation for the SNAP-25 gene polymorphism. The NAA, Cr, and Cho levels in the ACC and PFC were measured using magnetic resonance spectroscopy (MRS). Following the evaluation, 10 mg of oral MPH was given to the patients, and the same metabolite levels were measured after 30 minutes.

RESULTS: The levels of NAA, Cr, and Cho in the PFC and ACC of patients with the SNAP-25 D*del* and *Mnl*I polymorphism genotypes did not significantly differ before and after the administration of MPH. However, in patients with the SNAP-25 DdeI polymorphism T/T genotype and the *Mnl*I polymorphism G/G genotype, there was a significant increase in NAA levels in the ACC after MPH treatment compared with before MPH treatment.

CONCLUSION: The present results suggest that the SNAP-25 D*del* and *Mnl*I polymorphisms might be associated with MPH-related changes in NAA levels in the ACC.

Key Words:
Adult ADHD, SNAP-25 gene, Magnetic resonance spectroscopy, Methylphenidate, Anterior cingulate cortex.

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, with estimated prevalence rates of 5.3% among children and 1-4% among adults[1]. Neuroimaging techniques play an important role in understanding the structural and functional changes related to ADHD in various brain areas[2]. Functional and structural neuroimaging studies have revealed changes in the corpus callosum, frontal lobes, parietal lobes, temporal cortex, cerebellar vermis, and basal ganglia[3,4]. Recent advances in these techniques have also provided the opportunity to further investigate the relationship of brain structures and their functions to psychostimulant drug treatments[5]. Functional neuroimaging studies have reported that regional bloodstream and glucose metabolism decrease in the prefrontal and cerebellar areas but increase in the parieto–occipital cortex in the resting state and that these levels return to normal after psychostimulant drug treatment[6]. Jin et al[7] found no significant changes

Corresponding Author: Ayse Nur Inci Kenar, MD; e-mail: drinci79@hotmail.com

in the N-acetyl aspartate (NAA)/creatine (Cr) ratio or choline (Cho)/Cr ratio after a single dose of methylphenidate HCl (MPH), whereas Wiguna et al[8] observed an increase in the NAA/Cr ratio in the prefrontal cortex (PFC) of ADHD patients treated with MPH (20 mg/day).

Regardless of the link between the serotonergic system and ADHD, genes associated with the dopaminergic system are generally implicated in this disorder[9]. Nevertheless, recent research has assumed that the problems in the synaptic gap in ADHD patients are not restricted to only dopamine but that there may also be problems in the regulation of neurotransmitter release and synaptogenesis[10]. Thus, several works have attempted to determine the genes that encode the presynaptic proteins involved in these processes[10]. For example, SNARE proteins play a role in the modulation of neurotransmitter release via vesicle-associated membrane protein 2 (synaptobrevin 2 or VAMP2), the syntaxin 1A protein, and synaptosomal-associated protein 25 kDa (SNAP-25)[11]. Of the genes that encode these proteins, the most commonly studied gene is SNAP-25. In fact, the associations between ADHD and the two polymorphisms of this gene (*Mnl*I and *Dde*I) have been extensively researched. There is a relationship between either or both the *Mnl*I and *Dde*I polymorphisms and ADHD[12-15].

Recent pharmacogenetic investigations have also indicated that there is a relationship between the SNAP-25 gene and ADHD. A study of spontaneously hypertensive rats (SHR) determined that the reduced synthesis of SNAP-25 mRNA in the PFC normalized following recurrent amphetamine injections[16]. Similarly, alterations in the bloodstream of the brain may be influenced by a single dose of a psychostimulant in ADHD patients with the SNAP-25 polymorphism[17]. Moreover, the SNAP-25 polymorphism might be related to the side effects of MPH and the treatment response to this drug[18].

The effects of various genetic changes in the brain function of individuals with ADHD have received little attention; indeed, there is a relative lack of data regarding this topic. The integration of data from different fields of research, such as brain imaging and genetics, is essential to improve understanding of the physiopathology underlying complex disorders, such as ADHD. However, the changes in the brain metabolites of patients with the SNAP-25 polymorphism in response to MPH have yet to be studied. Thus, the present study aimed to evaluate the relationship between the SNAP-25 gene polymorphism and the effects of MPH use on NAA, Cr, and Cho levels in the anterior cingulate cortex (ACC) and dorsolateral PFC (DLPFC) using magnetic resonance spectroscopy (MRS) in adult ADHD patients.

Patients and Methods

Study Design

The present research was approved by the local Institutional Review Board and performed in accordance with the principles of the Helsinki Declaration; written informed consent was obtained from all subjects. A total of 60 patients between 18 and 60 years of age who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for adult ADHD were included in this study. All patients were recruited from the same clinic and were of Turkish origin. Patients with accompanying neurological and/or chronic diseases, intellectual disabilities, psychotic disorders, a psychiatric disorder due to organic factors, or who were illiterate were excluded from the study.

All patients were evaluated with the Adult ADHD Diagnosis and Evaluation Scale and the Wender Utah Rating Scale (WURS); the validity and reliability of the WURS for Turkish individuals were established by Oncu et al[19] based on a threshold score of 36. The validity and reliability of the Adult Attention Deficit Disorder (ADD)/ADHD DSM-IV-based Diagnostic Screening and Rating Scale for Turkish individuals were established by Gunay et al[20] Patients who scored 36 points or more on the WURS and gave an answer of 2 or 3 points to at least six of the nine questions in the first and/or second parts of the Adult ADHD Diagnosis and Evaluation Scale were diagnosed with ADHD.

Magnetic Resonance Spectroscopy

The present work was performed using a 1.5 Tesla magnetic resonance device (GE Medical System; Milwaukee, WI, USA) with a standard head coil and the following magnetic resonance protocol: horizontal plane = 10 mm thickness, TR/TE = 3000/88.2, FOV = 10, matrix = 512 × 512, and next = 1. T2-weighted fast spin echo (FSE) sequences were obtained using the aforementioned parameters, and MRS was performed using a single-voxel *(^{1}H-voxel)* technique in the ACC and DLPFC areas. The volume of interest was manually and visually placed on the related

areas with an awareness of containing related brain tissue and the predominantly determined areas. A chemical shift selective pulse (CHESS) process was used to inhibit water-derived signals, and then a point-resolved spectroscopy technique was employed (TR/TE = 3000/35). Consequently, the short-time TE spectrums were obtained from the volumes of interest in the ACC and DLPFC areas, and the metabolite ratios were evaluated using the General Electric Software Spectral Analysis Programme. An H^1 MRS analysis was performed by an expert radiologist, and the NAA, Cho, and Cr values were measured in the ACC and DLPFC areas. Then, oral MPH (10 mg) was given to the patients, and the NAA, Cho, and Cr values were measured again after an interval of 30 minutes.

DNA Isolation and Molecular Analysis

DNA was isolated from peripheral blood leukocytes using a standard phenol/chloroform method and then genotyped with a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The PCR was performed with an automated thermal cycler (Veriti, Applied Biosystems; Foster City, CA, USA) using the sense primer 5'-TTCTCCTC-CAAATGCTGTCG-3' and the antisense primer 5'-CCACCGAGGAGAGAAAATG-3' to amplify of the SNAP-25 gene. The PCR-RFLP assay was used to determine the occurrence of the SNAP-25 gene (GenBank Accession Number D21267) *Dde*I (rs1051312) and *Mnl*I (rs3746544) polymorphisms.

Statistical Analysis

All data were analyzed using the IBM Statistical Package for Social Sciences v16 (SPSS Inc., Chicago, IL, USA), and the Kolmogorov-Smirnov test was used to test for normality. The Kruskal-Wallis test was used to compare continuous variables and independent samples, the Wilcoxon t-test was used to assess dependent samples, and the Mann-Whitney U-test was used to compare data between the groups. A p-value < 0.05 was considered to indicate statistical significance.

Results

A total of 60 patients (48 males and 12 females) with a mean age of 28.98 ± 7.66 years (range: 18 to 59 years) met the eligibility criteria for this study. The distribution of the SNAP-25 gene D*del* polymorphism genotype among the patients was as follows: T/T (n = 41, 68.3%), T/C (n = 16, 26.7%), and C/C (n = 3, 5.0%). The distribution of the SNAP-25 gene *Mnl*l polymorphism genotype among the patients was as follows: T/T (n = 22, 36.7%), T/G (n = 27, 45.0%), and G/G (n = 11, 18.3%).

Prior to the initiation of MPH therapy, the levels of NAA, Cr, and Cho did not significantly differ in patients with the SNAP-25 D*del* polymorphism genotypes, ($p > 0.05$; Table I). Similarly, there were no significant differences among the SNAP-25 D*del* polymorphism genotypes with respect to NAA, Cr, and Cho levels

Table I. Distributions of N-acetyl-aspartate, creatine, and choline levels among patients with the SNAP-25 Ddel polymorphism genotypes before and after methylphenidate use.

			T/T (n = 41) mean ± SD	T/C (n = 16) mean ± SD	C/C (n = 3) mean ± SD	*p*-value*
NAA levels	Before	Prefrontal cortex	70.24 ± 14.44	62.44 ± 12.03	69.00 ± 14.11	0.204
	MPH	Anterior cingulate cortex	64.83 ± 15.26	62.88 ± 12.46	65.01 ± 15.72	0.956
	After	Prefrontal cortex	71.34 ± 15.67	64.38 ± 12.44	59.33 ± 7.10	0.199
	MPH	Anterior cingulate cortex	68.27 ± 13.48	64.56 ± 8.12	56.67 ± 5.13	0.174
Creatine levels	Before	Prefrontal cortex	41.73 ± 7.51	38.75 ± 4.64	35.67 ± 6.03	0.185
	MPH	Anterior cingulate cortex	42.83 ± 8.36	41.69 ± 6.63	37.33 ± 8.96	0.759
	After	Prefrontal cortex	42.20 ± 8.62	40.31 ± 7.28	37.67 ± 5.77	0.557
	MPH	Anterior cingulate cortex	43.46 ± 6.95	43.88 ± 7.54	39.00 ± 2.00	0.334
Choline levels	Before	Prefrontal cortex	43.24 ± 9.22	37.88 ± 8.67	36.00 ± 2.65	0.063
	MPH	Anterior cingulate cortex	38.59 ± 9.79	37.31 ± 8.01	38.00 ± 10.00	0.975
	After	Prefrontal cortex	42.15 ± 9.89	38.44 ± 8.02	35.33 ± 5.13	0.322
	MPH	Anterior cingulate cortex	38.39 ± 7.45	37.69 ± 6.90	29.00 ± 4.36	0.113

MPH = Methylphenidate HCl; NAA = N-acetyl aspartate. *Kruskal–Wallis test was performed. A p-value < 0.05 was considered to indicate statistically significance.

after MPH therapy ($p > 0.05$; Table I). There was a significant increase in NAA levels in the ACC of patients with the SNAP-25 D*del* polymorphism T/T genotype after MPH use relative to prior to MPH therapy ($p = 0.038$; Figure 1). However, the changes in NAA levels in the other SNAP-25 D*del* polymorphism genotypes after MPH therapy were not statistically significant ($p > 0.05$). The levels of NAA, Cr, and Cho did not significantly differ among patients with the SNAP-25 *Mnl*l polymorphism genotypes before MPH therapy relative to after MPH therapy ($p > 0.05$; Table II). However, patients with the SNAP-25 *Mnl*l polymorphism G/G genotype showed a significant increase in NAA levels in the ACC after MPH therapy compared with before MPH therapy ($p = 0.035$; Figure 2). There were no statistically significant changes in NAA levels in the other SNAP-25 *Mnl*l polymorphism phenotypes after MPH use ($p > 0.05$).

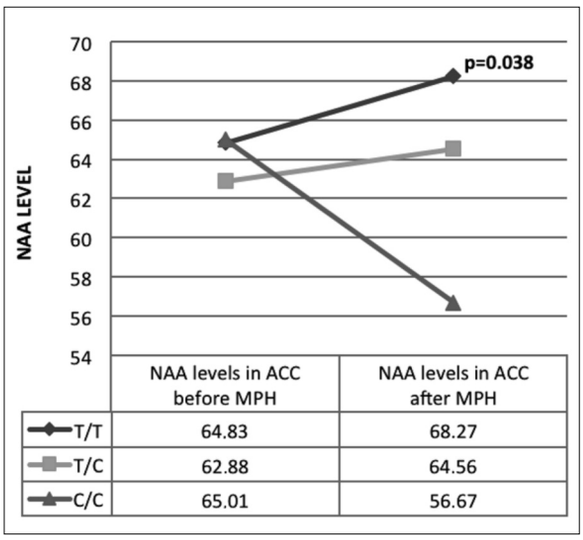


Figure 1. N-acetyl-aspartate levels in the anterior cingulate cortex of patients with the SNAP-25 Ddel polymorphism before and after methylphenidate use.

Discussion

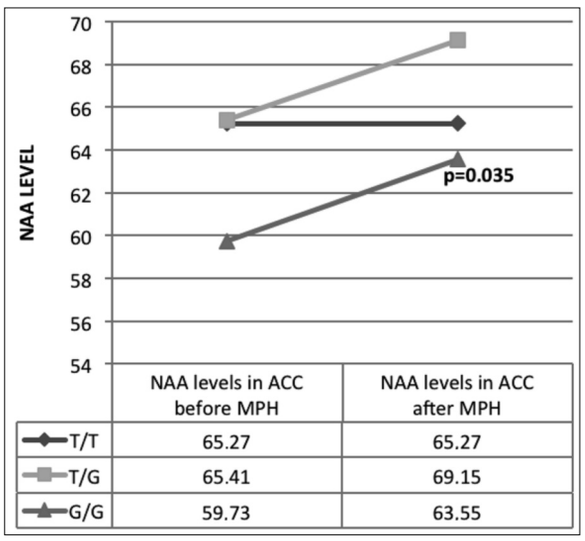
MRS has been used to determine the differential diagnoses of many disorders that actively influence neurodegenerative processes. Because NAA is as a marker of neuronal integrity, a low NAA/Cr ratio is associated with neuronal loss or damage. Cho reflects membrane integrity, and an increased Cho level or Cho/Cr ratio indicates an aggravation of cellular destruction, myelin destruction, gliosis, and/or inflammation. Additionally, Cr is a relatively constant factor involved in cellular energy metabolism[21].

Wiguna et al[8] observed an increase in the NAA/Cr ratio in the PFC of ADHD patients using MPH (20 mg/day) and suggested that these changes were due to functional amelioration and increases in neuroplasticity. Hesslinger et al[22] reported a decrease in NAA levels in the left DLPFC of hyperactive subtypes compared with

Table II. Distributions of N-acetyl-aspartate, creatine, and choline levels among patients with the SNAP-25 Mnll polymorphism genotypes before and after methylphenidate use.

			T/T (n = 22) mean ± SD	T/G (n = 27) mean ± SD	G/G (n = 11) mean ± SD	*p*-value*
NAA levels	Before MPH	Prefrontal cortex	67.36 ± 12.83	68.04 ± 16.15	69.73 ± 11.54	0.778
		Anterior cingulate cortex	65.27 ± 11.33	65.41 ± 17.81	59.73 ± 9.78	0.294
	After MPH	Prefrontal cortex	65.96 ± 12.23	71.22 ± 17.95	69.00 ± 11.10	0.506
		Anterior cingulate cortex	65.27 ± 10.63	69.15 ± 13.88	63.55 ± 10.42	0.257
Creatine levels	Before MPH	Prefrontal cortex	40.36 ± 5.26	41.15 ± 8.93	39.91 ± 4.01	0.899
		Anterior cingulate cortex	42.50 ± 7.48	42.37 ± 9.44	41.46 ± 4.55	0.936
	After MPH	Prefrontal cortex	39.82 ± 5.07	43.04 ± 10.86	40.91 ± 4.25	0.654
		Anterior cingulate cortex	43.09 ± 5.07	44.37 ± 8.33	41.36 ± 6.64	0.787
Choline levels	Before MPH	Prefrontal cortex	39.32 ± 8.91	42.07 ± 9.62	44.18 ± 8.38	0.196
		Anterior cingulate cortex	37.68 ± 10.00	39.04 ± 9.45	37.27 ± 7.49	0.859
	After MPH	Prefrontal cortex	40.18 ± 10.03	41.15 ± 9.33	41.27 ± 8.90	0.771
		Anterior cingulate cortex	38.55 ± 7.87	38.19 ± 6.90	35.00 ± 7.63	0.402

MPH= Methylphenidate HCl; NAA= N-acetyl aspartate. *Kruskal-Wallis test was performed. A *p*-value < 0.05 was considered to indicate statistical significance.



	NAA levels in ACC before MPH	NAA levels in ACC after MPH
T/T	65.27	65.27
T/G	65.41	69.15
G/G	59.73	63.55

Figure 2. N-acetyl-aspartate levels in the anterior cingulate cortex of patients with the SNAP-25 Mnll polymorphism before and after methylphenidate.

inattentive subtypes in a MRS research of adult ADHD patients. Decreased NAA levels have been associated with neuronal loss or functional impairments in neuronal activity[22]. A study of neurometabolite changes in various brain areas, including circuits associated with the DLPFC, after 2 months of MPH or atomoxetine treatment in children with ADHD found that there were reductions in NAA levels and in the NAA/Cr ratio in the left DLPFC but an increase in the Cho/Cr ratio in the right DLPFC after atomoxetine treatment[23]. Additionally, combined treatment with glutamate and glutamine (Glu+Gln) and Glu+Gln with Cr increased the remaining white matter after MPH treatment[23]. These authors speculated that atomoxetine reduces the hyperfunction of neurons in the DLPFC and that MPH leads to increases in the activity of cortical glutamatergic neurons which, in turn, enhances tonic dopamine release in the mesocortical system.

A meta-analysis of 16 MRS investigations reported no significant differences in NAA levels in adults with ADHD, but children with ADHD had significantly higher NAA levels[24]. The authors also found a significant correlation between normal levels of NAA in the medial PFC (mPFC) and advanced age, which suggests that alterations in NAA in the mPFC according to age may be a potential underlying neuropsychiatric factor associated with changes in ADHD symptoms. However, an evaluation of ACC studies[25] that included 28 adult ADHD patients and 28 healthy controls did not find any differences in the NAA/Cr ratio, and a comparison of adult ADHD patients and control subjects did not find any significant differences in NAA levels in the ACC[26].

Recent pharmacogenetic researches have found an association between the *Mnl*I and *Dde*I polymorphisms of the SNAP-25 gene and ADHD. A functional near-infrared spectroscopy (fNIRS) study by Oner et al[17] that included 16 children with ADHD and 15 adults with ADHD determined that hemodynamic alterations in the brain stimulated by MPH might be associated with the SNAP-25 gene *Mnl*I T/T and *Dde*I T/T genotypes. These authors proposed that their results were correlated with the findings of Barr et al[13] and that a combination of the *Dde*I and *Mnl*I polymorphisms of the SNAP-25 gene might be important in ADHD[17].

To the best of our knowledge, no MRS study has investigated changes in cerebral metabolites following MPH therapy based on the SNAP-25 polymorphisms. In the present study, there were no significant differences in NAA levels among the patients with the SNAP-25 D*del* polymorphism genotypes prior to and after MPH therapy, but a significant increase in NAA levels was detected in the ACC of patients with the SNAP-25 D*del* T/T genotype after MPH therapy. Because the T/T genotype was detected in 68.3% of the study group, it is possible that MPH is more effective in ADHD patients with this polymorphism. A Turkish work that investigated the correlation between the SNAP-25 D*del* polymorphism and ADHD found that the T/T genotype was the most frequently identified genotype (73.5%)[15]. In our study, there were no significant correlations between MPH use and Cr and Cho levels in patients with the SNAP-25 D*del* polymorphism genotype.

Here, we study also found that patients with the SNAP-25 *Mnl*I polymorphism G/G genotype exhibited significant increases in NAA levels in the ACC after MPH use. The prevalences of the T/T (n = 22), T/G (n = 27), and G/G (n = 11) genotypes were 36.7%, 45%, and 18.3%, respectively. Herken et al[15] revealed similar incidence rates when the correlation between the SNAP-25 polymorphism and ADHD was investigated. However, although the G/G genotype was the least commonly detected genotype, higher Wender-Utah and Turgay subscale scores were reported in ADHD patients with this genotype[13]. When these outcomes were taken into consideration,

the individuals with G/G genotypes had more severe symptoms and, accordingly, a greater degree of disrupted neuronal integrity. Thus, MPH likely induces relatively higher NAA increases in individuals with this genotype.

The present work has several limitations that should be noted. It is possible that there is a potential long-term impact of drug treatment on the metabolite levels that were assessed by MRS in this study. Additionally, it was impossible to exclude the effects of smoking on the treatment response to MPH, and the present study did not include a control group. That is, it employed low TESLA units in the cranial magnetic resonance technique, and evaluated only a unilateral field. Thus, the neuropathologies underlying ADHD require further research with control groups to minimize the effects of age and gender as well as with neuroimaging techniques with higher resolution. Additionally, only a limited number of pharmacogenetic studies have been performed on individuals with ADHD.

This study is the first to investigate cerebral metabolites from a pharmacogenetic perspective.

Conclusions

ADHD is a neuropsychiatric disorder caused by dysfunction within frontostriatal pathways and genetic factors that play a role in its etiopathogenesis. The present demonstration of the correlation between the reaction to MPH and some variants of the SNAP-25 gene may aid in future studies that attempt to predict responses to MPH. Research investigating SNAP-25 genes, genes related to the predisposition for ADHD, and the response to stimulant treatment may open new horizons for the diagnosis and treatment of ADHD.

Conflict of Interest

Funding was provided by the Commission of Scientific Research Projects.

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