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Association of the G>A (rs6265) polymorphism in the brain derived neurotrophic factor gene (BDNF) with post-training changes in Caucasian women

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Abstract

The brain-derived neurotrophic factor (*BDNF*) rs6265 (G196A; Val66Met) polymorphism has been associated with obesity and type 2 diabetes, with contradictory results involving either A or G as the risk allele. The main aim of this study was to examine whether the BDNF rs6265 polymorphism would influence the efficiency of a training program. An additional aim was to determine whether selected polymorphism can be used as a genetic marker for obesity-related parameters. We studied the genotype distribution in a group of 160 Caucasian females in whom body mass and composition parameters, lipid profile, and glucose levels were measured before and after the 12-week aerobic training program. The majority of obesity-related parameters significantly changed during the intervention (main effect of training); however, the training response was not modulated by genotype (non-significant genotype × training interactions). We also did not find an effect of genotype on selected parameters. Our study showed that the rs6265 polymorphism does not affect the efficiency of the applied training program and is not a good genetic marker for assessing the obesity-related parameters in the studied population. However, we confirmed that regular physical activity is associated with an improvement in obesity-related parameters, which is an important observation for public health.

Keywords

sport genetics, obesity, physical activity, BDNF, genotype × training interaction

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Article

Association of the G>A (rs6265) polymorphism in the brain derived neurotrophic factor gene (*BDNF*) with post-training changes in Caucasian women

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Abstract: The brain-derived neurotrophic factor (*BDNF*) rs6265 (G196A; Val66Met) polymorphism has been associated with obesity and type 2 diabetes, with contradictory results involving either A or G as the risk allele. The main aim of this study was to examine whether the BDNF rs6265 polymorphism would influence the efficiency of a training program. An additional aim was to determine whether selected polymorphism can be used as a genetic marker for obesity-related parameters. We studied the genotype distribution in a group of 160 Caucasian females in whom body mass and composition parameters, lipid profile, and glucose levels were measured before and after the 12-week aerobic training program. The majority of obesity-related parameters significantly changed during the intervention (main effect of training); however, the training response was not modulated by genotype (non-significant genotype × training interactions). We also did not find an effect of genotype on selected parameters. Our study showed that the rs6265 polymorphism does not affect the efficiency of the applied training program and is not a good genetic marker for assessing the obesity-related parameters in the studied population. However, we confirmed that regular physical activity is associated with an improvement in obesity-related parameters, which is an important observation for public health.

Keywords: sport genetics, obesity, physical activity, BDNF, genotype × training interaction.

1. Introduction

Human obesity is a serious medical abnormality worldwide that has a well-confirmed genetic basis, but requires behavioral, developmental, and/or environmental factors to develop [1–3]. Numerous studies have shown the role of the lifestyle factor, including caloric intake and physical activity, in weight control [4–6]. However, the problem lies in defining the specific genes and polymorphisms related to obesity and describing the

mechanisms by which they exert their effects [2]. A complex meta-analysis of genome-wide association studies (GWAS) for the body mass index (BMI) in ~700,000 individuals of European ancestry revealed 941 near-independent single nucleotide polymorphisms (SNPs) associated with BMI. These variants are frequently localized in genes involved in neurogenesis and more generally involved in the development of the central nervous system (CNS) [7]. Thus, the gene encoding brain derived neurotrophic factor (BDNF) seems to be a promising genetic marker for both a risk of developing obesity and post-training changes in selected body mass, body composition, and biochemical parameters of energy metabolism.

BDNF belongs to the neurotrophin family of nerve growth factors (NGF) and is widely expressed in CNS. It plays a key role in the proliferation, differentiation, survival, outgrowth, and death of central and peripheral neurons [8]. In addition, its expression in the hypothalamus, a key region of the brain involved in controlling appetite, seems to affect balance between energy consumption and energy expenditure [9]. Mechanistically, BDNF is supposed to function as a downstream regulator of the leptin proopiomelanocortin pathway, which controls body mass and general metabolic fitness [10]. Thus, polymorphisms of the *BDNF* gene, which is located at chromosomal position 11p14.1, may affect energy homeostasis and, consequently, lead to the development of the obese phenotype. One common polymorphism rs6265 present in the coding region (exon 11) of the *BDNF* gene involves G→A transition at the nucleotide position 196 (G196A), which in turn results in valine to methionine substitution at the amino acid position 66 (Val66Met) of the N-terminal domain region of pro-BDNF. This single nucleotide substitution affects BDNF expression, localization, and signal transduction contributing to alterations in the phenotype [11–13]. Numerous studies have associated this SNP with early seizures, bipolar affective disorders, obsessive-compulsive disorders, eating disorders, and obesity [8, 14–18]. The G allele has been usually connected with increased risk for obesity and type 2 diabetes, as well as appearing to predict weight regain in treatment studies [18–20]. However, some authors have shown a lack of association or even the opposite direction of association [15, 22, 23].

Although, the association of *BDNF* with overweight and obesity in both children and adults has been observed in diverse ethnic populations, including European, Asian, and Hispanic individuals [18], a connection between this gene, physical activity, and obesity-related traits is still unclear. Therefore, the main aim of this study was to examine whether the rs6265 polymorphism in the *BDNF* gene would influence the efficiency of a 12-week training program. An additional aim was to determine whether the selected polymorphism can be used as a genetic marker to determine the predisposition to the development of obesity and the unfavorable metabolic properties associated with it.

2. Materials and Methods

2.1. Participants

One hundred sixty Polish Caucasian females (age: 21 ± 1 years) were selected for the study. The inclusion criteria were as follows: low level of physical activity (the Global Physical Activity Questionnaire was used); no musculoskeletal, neuromuscular or metabolic diseases; having refrained from using medications and supplements for 6 months before the experiment and being nonsmokers. Participants received an information sheet and a written consent form. The experiment was approved by the Ethics Committee of the Regional Medical Chamber in Szczecin (no. 09/KB/IV/2011 and 01/KB/VI/2017).

2.2. Dietary and training program

Participants took part in a dietary program and were expected to keep a balanced diet based on their personal dietary plan, which was established during a nutritional meeting involving a recommendation of an adequate diet matched with personal energy needs and nutritional status. The medium daily macronutrient ratio was proposed

(expressed as a percentage of total calories): 45–65% from carbohydrates, 20–35% from fat (reducing the intake of saturated fats and increasing the intake of unsaturated fats), and 10–20% from proteins. The women were also asked to maintain a daily cholesterol intake of less than 300 mg, with a minimum dietary fiber intake of 25 g.

The proper training was preceded by a week-long familiarization stage (3 units, 30 min each). Then, a 12-week (36 units, 60 min each) experimental training program was divided into 4 stages (3 weeks each) of increasing intensity. Each training unit included a warm-up (10 min), the main low and high impact aerobic exercises (43 min), and a cool-down phase (7 min). The training program was previously described in detail [24].

2.3. Body mass and body composition measurements

Before and after the completion of the training program, the selected body mass and body composition parameters were assessed with the bioimpedance method using an electronic scale, Tanita TBF 300 M (Arlington Heights, Illinois, United States), as previously described [24]. The investigated parameters are shown in Table 1.

2.4. Biochemical analyses

Biochemical analyses were also performed before and after the training program. Fasting blood samples were obtained from the elbow vein in the morning. The analyses were performed immediately after the blood collection, as previously described in detail [24]. The chosen parameters received using the Random Access Automatic Biochemical Analyzer for Clinical Chemistry and Turbidimetry A15 (BioSys-tems S.A., Barcelona, Spain) are given in Table 1.

Table 1. Investigated body mass, body composition, and biochemical parameters

Body mass and body composition parameters		
body mass	BM	kg
body mass index	BMI	kg/m^2
basal metabolic rate	BMR	kJ
fat mass	FM	kg
fat free mass	FFM	kg
fat mass percentage	%FM	%
total body water	TBW	kg
Biochemical parameters		
total cholesterol	TC	mg/dL
triglycerides	TGL	mg/dL
high density lipoprotein	HDL	mg/dL
low density lipoprotein	LDL	mg/dL
blood glucose	BG	mg/dL

2.5. Genetic analyses

Genomic DNA was extracted from the buccal cells using a GenElute Mammalian Genomic DNA Miniprep Kit (Sigma, Steinheim, Germany) according to the manufacturer's recommendation. All samples were genotyped in duplicate using TaqMan® Pre-Designed SNP Genotyping Assays (Applied Biosystems, Waltham, MA, USA) on a C1000 Touch Thermal Cycler (Bio-Rad, Feldkirchen, Germany) instrument according to the manufacturer's procedures. The assay C__11592758_10 included primers and fluorescently labeled (FAM and VIC) probes to discriminate the *BDNF* alleles.

2.6. Statistical analyses

Statistical analysis was performed in R statistical software (R Core Team, 2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Hardy-Weinberg equilibrium was evaluated using an exact test implemented in the R package SNPassoc (version 2.0-18). A linear mixed effect model was used for association analysis between rs6265 genotypes and outcome variables over time. The R packages effects (version 4.2-2) and marginal effects (version 0.15.1) were used to visualize predictor effects and estimate contrasts, respectively.

3. Results

Genotype frequencies of the *BDNF* polymorphism: AA – 43 (26.875%), AG – 79 (49.375%), GG – 38 (23.750%) were tested for Hardy-Weinberg equilibrium, and no significant deviations from theoretical frequencies were found ($p = 0.875$).

Body mass and composition parameters, lipid profile, and glucose levels measured before and after the training period with respect to the *BDNF* genotype are presented in Table 2. Most parameters (BM, BMI, BMR, %FM, FM, FFM, TBW, HDL, and BG) significantly changed during the intervention (main effect of training); however, the training response was not modulated by genotype (non-significant genotype × training interactions). We also did not find an effect of genotype on selected parameters.

Table 2. Contrast of estimated marginal effects for the time and rs6265*

Parameter	Term	Contrast	Estimate	SE	P	95% CI
BM	Time	After – Before	-0.763	0.133	< 0.001	-1.02 -0.503
	rs6265	AG – AA	0.671	1.48	0.651	-2.23 3.58
		GG – AA	-0.136	1.74	0.938	-3.54 3.27
BMI	Time	After – Before	-0.233	0.0419	< 0.001	-0.315 -0.151
	rs6265	AG – AA	-0.143	0.464	0.758	-1.05 0.767
		GG – AA	-0.255	0.544	0.639	-1.32 0.812
BMR	Time	After – Before	-38.3	9.16	< 0.001	-56.2 -20.3
	rs6265	AG – AA	43.3	62.1	0.486	-78.5 165
		GG – AA	12.9	72.9	0.859	-129.9 156
%FM	Time	After – Before	-1.34	0.179	< 0.001	-1.69 -0.986
	rs6265	AG – AA	0.158	1.06	0.882	-1.92 2.24
		GG – AA	0.646	1.24	0.604	-1.79 3.09
FM	Time	After – Before	-0.954	0.131	< 0.001	-1.21 -0.697
	rs6265	AG – AA	0.463	0.986	0.639	-1.47 2.39
		GG – AA	0.439	1.156	0.704	-1.83 2.70
FFM	Time	After – Before	0.426	0.0994	<0.001	0.231 0.621
	rs6265	AG – AA	-0.018	0.620	0.977	-1.23 1.198
		GG – AA	-0.577	0.727	0.428	-2.00 0.849
TBW	Time	After – Before	0.336	0.111	0.00241	0.119 0.553
	rs6265	AG – AA	-0.00768	0.472	0.987	-0.933 0.918
		GG – AA	-0.39983	0.554	0.470	-1.485 0.686

Parameter	Term	Contrast	Estimate	SE	P	95% CI
TC	Time	After – Before	-1.65	1.69	0.329	-4.96 1.66
	rs6265	AG – AA	1.30	4.61	0.777	-7.73 10.3
		GG – AA	1.07	5.41	0.843	-9.53 11.7
TGL	Time	After – Before	2.86	2.37	0.226	-1.77 7.5
	rs6265	AG – AA	2.16	5.23	0.679	-8.08 12.4
		GG – AA	3.87	6.13	0.528	-8.15 15.9
HDL	Time	After – Before	-4.12	0.894	<0.001	-5.87 -2.37
	rs6265	AG – AA	-0.442	2.33	0.850	-5.01 4.13
		GG – AA	0.363	2.74	0.895	-5.00 5.72
LDL	Time	After – Before	1.97	1.62	0.223	-1.2 5.14
	rs6265	AG – AA	1.2827	3.94	0.745	-6.44 9.01
		GG – AA	-0.0669	4.62	0.988	-9.13 9.00
BG	Time	After – Before	-2.82	0.868	0.00114	-4.53 -1.12
	rs6265	AG – AA	1.32	1.61	0.412	-1.84 4.48
		GG – AA	1.18	1.89	0.531	-2.52 4.89

* time by rs6265 interaction was not significant for any parameter, SE – standard error, 95% CI – confidence interval, the level of statistical significance was set at $p < 0.05$

4. Discussion

To answer the question of whether the common *BDNF* rs6265 polymorphism influences the post training changes in selected body mass and composition parameters, lipid profile, and glucose levels, we assessed the allele and genotype distribution in young healthy women participating in 12-week aerobic training. The obtained results provide evidence that the rs6265 polymorphism in the *BDNF* gene does not affect the efficiency of a training program. In addition, we have shown that this polymorphism is not a good genetic marker for assessing the obesity-related parameters in the studied group.

Previous studies have shown the BDNF binds to its tropomyosin-related kinase B (TrkB) receptor [25] and regulates food intake and energy metabolism by central and peripheral actions, as well as affects the physical activity level, hyperactivity, anxiety, and hyperphagia [26, 27]. According to these findings, lower BDNF levels were found in obese, compared to normal weight participants [28]. However, some studies showed opposite results [29]. One possible explanation for these inconsistent observations could be differences in physical activity and sedentary behavior, which can greatly affect the interpretation of the noticed associations [18]. Consequently, variants in the *BDNF* gene may be responsible for obesity and eating disorders [8, 16, 18]. A meta-analysis study, which has been conducted to evaluate the association of the *BDNF* gene polymorphisms with BMI, has shown that the rs6265, rs925946, rs10501087, and rs988712 polymorphisms significantly increased the risk of an excess of human body mass gain, indicating that these variants may be involved in the development of obesity [8]. The rs6265 (G196A or Val66Met) is a well-characterized functional SNP that influences intracellular trafficking of BDNF mRNA to dendrites, activity-dependent secretion, and subsequently hippocampal function in transgenic mice and in humans [12]. In addition, G→A transition eliminates a CpG methylation site (the G/Val allele has a CpG at this position while the A/Met allele does not), allowing for epigenetic association that may in part explain environmentally influenced phenotypes such as the obesity phenotype [30]. In the BDNF protein, the methionine substitution interrupts a sortilin binding site that disrupts activity-dependent secretion of BDNF at the synapse. The amino acid substitution also causes different signal transduction events and functional results among the three isoforms of the BDNF

peptides. This change directly modifies the BDNF precursor (proBDNF), subsequent signaling, and confers an acquired binding ability of the cleaved prodomain to sortilin related Vps10p-domain sorting receptor 2 (SorCS2). The Met proBDNF variant shows decreased binding to sortilin, changed intracellular trafficking, and a reduction in the activity-dependent secretion of BDNF. This SNP even impacts downstream signaling of the otherwise identical "mature" portion, albeit indirectly via aberrant compartmentalization and dysregulation of the balance of proBDNF/p75 neurotrophin receptor ($p75^{NTR}$) and mature BDNF/TrkB signaling complexes [13, 31].

With regard to obesity-related parameters, the majority of studies, particularly those with larger sample sizes, have shown the G allele (Val66 variant) to be associated with increased BMI in both children and adults across diverse ethnic populations. The G allele also appears to predict body mass regain in interventional studies [18]. In patients with impaired glucose tolerance in the Diabetes Prevention Program (DPP) and patients with diabetes in the Look Action for Health in Diabetes (AHEAD) study, the G allele was connected with greater body mass regain across interventions, reaching significance in the DPP [32] and borderline significance in the Look AHEAD [33]. However, some studies have shown a lack of association or even inverse association, with the A allele (Met66 variant) being identified as the obesity risk allele [15, 22, 23]. Our results also did not show any relationship between the SNP and obesity-related traits or training effectiveness. Differences in sample sizes and selection, methodology, variation in study duration, ethnicity, age, body mass of participants, moderate genetic effects, and other characteristics may explain the inconsistent results [8]. In addition, epigenetic mechanisms related to environmental factors, such as physical activity and diet, modulate the effect of *BDNF* rs6265, thus weakening the effect of the rs6265 genotype [30].

We have also shown that the majority of the tested parameters changed significantly during the training program. We noticed a favorable decrease in BM, BMI, BMR, %FM, FM, TC, and BG, as well as an increase in FFM and TBW. Thus, we confirmed that living a physically active lifestyle is associated with an improvement in obesity-related parameters, which is still an important observation for public health. This observation is consistent with numerous studies that have clearly indicated that systematic physical activity has significant benefits for human health, including a reduction of the risk of cardiovascular diseases, type 2 diabetes, excessive body weight gain because of an increase in adipose tissue, and improved obesity-related parameters [34, 35]. However, the unfavorable changes in some lipid profile parameters, such as an increase in TGL and LDL, and a decrease in HDL were also noticed. Other authors confirmed that the effect of exercise on lipid profile is inconsistent in humans, and there are even results opposite to expected [36, 37]. Wang and Xu [36] explained that the differences in results may be due to variations in people's weight. Some studies showed that aerobic exercise alone did not change the lipid profile levels unless the weight during this period also changed. O'Donovan et al. [37] suggested that changes in coronary heart disease risk factors such as TC, TGL, LDL, and HDL concentrations are influenced by exercise intensity. They showed that high-intensity training is more effective than moderate-intensity training at the same energy cost. In a study including 34 young women divided into three groups: underweight, normal weight, and overweight, participating in a 12-week training program, Kostrzewa-Nowak [38] showed favorable changes in body compositions together with a significant decrease in TGL, TC, HDL, and LDL concentrations only in the overweight group (in underweight and normal weight groups they did not observe those changes).

5. Conclusions

In conclusion, although BDNF is an important regulator of energy balance, the common *BDNF* rs6265 polymorphism does not affect the efficiency of the applied training program and is not a good genetic marker for assessing the obesity-related parameters in the studied population. We have also demonstrated that the majority of tested parameters significantly changed during the training program. Thus, we confirmed that living a

physically active lifestyle is associated with an improvement in most obesity-related parameters, which is an important observation for public health.

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