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Consequences of the rs6265 (Val66Met) polymorphism in the BDNF gene in selected mental disorders and sport

Konsekwencje polimorfizmu rs6265 (Val66Met) genu BDNF w wybranych zaburzeniach psychicznych i sporcie

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Abstract

Introduction: Brain-derived neurotrophic factor (BDNF) is a polypeptide of 247 amino acid residues and is widely distributed throughout the central nervous system of the CNS. It plays an important role in the survival, differentiation, growth, and development of neurons in the central nervous system. The human BDNF gene is located on chromosome 11 in the p13-14 region and covers approximately 70 kb. The gene has a complex structure as it consists of 11 exons (I-IX, plus Vh and VIIIh) and nine functional promoters. BDNF expression in the brain is relatively low but it is found in most major regions of the brain.

Material and methods: The gene encoding the brain-derived neurotrophic factor BDNF has many polymorphisms, but one of them mainly attracts the attention of researchers. This is a common, non-conservative polymorphism - rs6265 - a single nucleotide SNP polymorphism that results in an amino acid change – valine (Val) to methionine (Met) - at codon 66.

Results: Polymorphism rs6265 is associated with many neuropsychiatric disorders, including depression or a higher risk of addiction, but it also determines other features, such as e.g. sports performance. Few studies are investigating the relationship between rs6265 polymorphism and predisposition to play sports.

Conclusions: The results on the effect of rs6265 BDNF polymorphic variants on the risk of depression and addition are inconsistent, indicating a significant association in some studies and none in others. Therefore, more studies are needed to determine how rs6265 affects gene expression and function.

Keywords: BDNF, polymorphism, depression, sport, addition

Streszczenie

Wstęp: Neurotroficzny czynnik pochodzenia mózgowego (BDNF) jest polipeptydem składającym się z 247 reszt aminokwasowych i jest szeroko rozpowszechniony w ośrodkowym układzie nerwowym (OUN) . Odgrywa ważną rolę w przeżyciu, różnicowaniu, wzroście i rozwoju neuronów w ośrodkowym układzie nerwowym człowieka. Ludzki gen BDNF znajduje się na chromosomie 11 w regionie p13-14 i obejmuje około 70 kb. Gen ma złożoną strukturę, ponieważ składa się z 11 eksonów (I-IX oraz Vh i VIIIh) i dziewięciu funkcjonalnych promotorów. Ekspresja BDNF w mózgu jest stosunkowo niska, ale występuje w większości głównych obszarów mózgu.

Materiał i metody: Gen kodujący neurotroficzny czynnik pochodzenia mózgowego BDNF ma wiele polimorfizmów, ale jeden z nich przede wszystkim przyciąga uwagę badaczy. Jest to powszechny, niekonserwatywny polimorfizm – rs6265 – polimorfizm pojedynczego nukleotydu SNP, który powoduje zmianę aminokwasu – waliny (Val) na metioninę (Met) – w kodonie 66.

Dyskusja: Polimorfizm rs6265 związany jest z wieloma zaburzeniami neuropsychiatrycznymi, w tym z depresją oraz uzależnieniami, a także determinuje inne cechy organizmu, takie jak np. osiągnięcia sportowe. Niewiele badań analizuje związek między polimorfizmem rs6265 a predyspozycją do uprawiania sportu.

Wnioski: Wyniki badań naukowych dotyczących wpływu wariantów polimorficznych rs6265 BDNF na ryzyko depresji i

uzależnień są niespójne. Dlatego potrzebne są dalsze eksperymenty, aby wiarygodnie określić, w jaki sposób rs6265 wpływa na ekspresję i funkcję genu.

Słowa kluczowe: BDNF, depresja, sport, uzależnienia, polimorfizm

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a polypeptide of 247 amino acid residues and is widely distributed throughout the central nervous system of the CNS. It plays an important role in the survival, differentiation, growth, and development of neurons in the central nervous system [1]. There is evidence that BDNF plays a role in the brain's reward system [2] and BDNF itself can elicit a reward effect that is similar to that induced by opioid drugs [3]. The main element of drug-enhanced behavior and related conditional phenomena is the mesolimbic projection of dopamine from the ventral tegmental area to the nucleus accumbens where dopamine receptors D3 (DRD3) dominate [4,5]. Research by Yixinet et al. [3] showed that BDNF can increase dopamine (DA) levels and increase the expression of DRD3, which can bind DA to generate partial physiological function.

2. Protein BDNF

The BDNF protein was discovered in 1982 by Barde et al. [6]. Research by Maison Pierre et al. showed that it contains 247 amino acids that are homologous with other neurotrophins at levels of ~ 50% ~. Like other neurotrophins, BDNF is translated into precursor forms that must undergo proteolysis to function properly. First, the preproBDNF isoform is translated and proteolyzed to form the proBDNF isoform. Then, if proBDNF is not cut into the endoplasmic reticulum or vesicles, it is secreted as a functional protein [7–9] which binds the p75 NTRsortilin receptor complex [10]. ProBDNF induces apoptosis by interacting with p75 and its coreceptor Sortilin [11]. However, proBDNF can undergo proteolysis to produce the mBDNF protein that binds to the TrkB receptor, leaving a truncated prodomain peptide sequence that was found to be a ligand per se, with functions that vary depending on the presence of the substitution in BDNF Val66Met [11].

The three functional isoforms of BNDFM (proBDNF, mBDNF, and prodomain) are expressed and induce independent biological effects. It follows that the amino acid sequence of BDNF retains functional compartmentalization. According to the Protein Family Database [14],there are three key domains in the BDNF amino acid sequence: 1) a signal domain at the position between residues 1-18; 2) a region of low complexity between residues 100-111 (within the BDNF prodomain); 3) the domain of the nerve growth factor (NGF) family (amino acids 133-246). The NGF domain contains most of the mBDNF sequences and underlines its functional specificity for the BDNF prodomain. According to the Protein Family Database, the BDNF signal domain is highly conserved between species [14]. There are also several post-translational modification (PTM) sites in the amino acid sequence of BDNF, incl. an N-glycosylation site at amino acid residue 121 [15]. Presumably, other PTMs are also present in the BDNF amino acid sequence, such as an N-myristoylation site at amino acid residues 14, 41, and 161, or an octapeptide at residues 79-86 [16]. However, except for the confirmed N-glycosylation of the BDNF prodomain [20,21], these PTMs have not been studied [17].

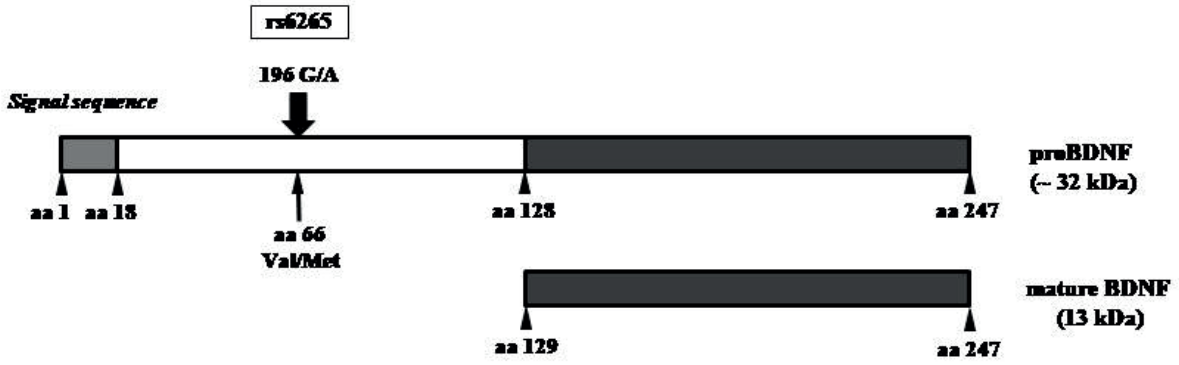

Figure 1. Structure of proBDNF and mature BDNF. Arrowheads indicate known protease cleavage sites involved in the processing to mature BDNF. The position of the single nucleotide polymorphism (rs6265, Val66Met) in human BDNF is indicated by arrows. This figure was modified from Zhang et.al.[13].

However, PTMs are believed to play a role in stabilizing the BDNF prodomain during intracellular processes [18].

3. Gene BDNF

The human BDNF gene is located on chromosome 11 in the p13-14 region and covers approximately 70 kb. The gene has a complex structure as it consists of 11 exons (I-IX, plus Vh and VIIIh) and nine functional promoters [19]. Each of these exons retains specific translation patterns and some contain inframe start codons that may shift the translation start site to modify the length of the translated BDNF peptide. Specifically: 1) exons VIII and VIIIh are always entangled with exons V; 2) exons II, III, IV, V, Vh, VI, and VIIIh are not translated; 3) exons I, VII contain ATG start sites that can modify the length of the n-terminus of proBDNF. Moreover, exons II, V, and VI have alternative splicing donor sites that can modify the length of the 5 'untranslated region (UTR) of BDNF transcripts. [20]. The functional significance of these alternative splicing events that modify UTR length has not yet been explored in detail. However, there is credible evidence that short BDNF UTR transcripts remain in the neuronal soma, while long BDNF UTR transcripts are targeted to dendrites where they play a significant role in dendritic morphology and long-term potentiation (LTP) [21]. In addition, BDNF long UTR transcripts suppress BDNF translation both at rest and during neuronal activity, while BDNF short UTR transcripts are highly sensitive to neuronal activity and seek to maintain active translation patterns to maintain basal BDNF protein production [22].

Very important was the discovery of the existence of the anti-BDNF (or BDNFOS0) gene. It encodes a series of BDNF antisense transcripts. This antisense strand creates an RNA duplex with the BDNF gene transcripts in vivo, which weakens their translation and limits the availability of the BDNF peptide. The discovery of the gene revealed an important post-transcriptional mechanism, which is responsible for maintaining BDNF functionality in the brain and other peripheral tissues [20].

4. Expression of the brain-derived neurotrophic factor BDNF

BDNF expression in the brain is relatively low but it is found in most major regions of the brain [23,24]. Even so, it is not expressed uniformly in all regions of the brain. Local assessments of BDNF mRNA concentration are not always the same with peptide concentrations in distinct populations of neurons. However, the expression profile shows the specificity of BDNF's mechanisms of action between and within brain regions, and that any stimulus-induced expression must be deliberately controlled by responsive regulatory elements [17].

An example is the regulation of BDNF by sex hormones, and especially by estrogens, which are expressed at many levels, including gene structure, molecular expression, and behavior. According to Sohrabja et al., the BDNF gene contains a sequence that has been identified as a possible element of the estrogen response [25]. Hill et al. described the sex differences for steroid sex hormone-dependent BDNF expression. Moreover, their results indicate that BDNF is sensitive to temporal fluctuations in estrogens, which are physiological [26]. It is known that women are more prone to disorders such as depression, so it is worth investigating the functional importance of BDNF and sex steroid hormones in disease processes [17]. The expression of BDNF may also be regulated during development. Research by Yang et al. suggests that proBDNF is present in greater amounts in the brain before adulthood, possibly to aid in developmental processes specific to this stage of development [27].

5. Consequences of genetic variation in BDNF

The gene encoding the brain-derived neurotrophic factor BDNF has many polymorphisms, but one of them mainly attracts the attention of researchers. This is a common, non-conservative polymorphism - rs6265 - a single nucleotide SNP polymorphism that results in an amino acid change – valine (Val) to methionine (Met) - at codon 66. Hence its popular name Val66Met. The Met allele of the SNP rs6265 has been shown to alter intracellular processing, trafficking, and packaging of proBDNF, and it consequently interferes with the activity-dependent secretion of mature BDNF in neurons [28,29].

It is associated with many neuropsychiatric disorders, including depression or a higher risk of addiction, but it also determines other features, such as e.g., sports performance.

5.1.1 SNP rs6265 in depression

Depression is a serious neuropsychiatric disorder that, according to the definition of the World Health Organization, is characterized by sadness, loss of interest and pleasure, guilt, low self-esteem, sleep, and appetite disorders, fatigue, and decreased concentration. Depression significantly affects the quality of life of patients and their ability to function in every area of life, both social and professional. Depression is the fourth most serious health problem in the world [30].

Major depressive disorder (MDD) is a complex, multifactorial disease of unknown pathogenesis that requires a combination of environmental and genetic factors to develop. The results on the effect of BDNF polymorphic variants on the risk of MDD are inconsistent, indicating a significant association in some studies and none in others. It is probably related to genotypic and phenotypic heterogeneity in different studied populations [31]. Table 1 presents an overview of publications

Table 1. The relationship of the rs6265 polymorphism of the BDNF gene and depression in different populations.

A study group with depression	Result	References
Malaysians; n=400	Carriage of the A / A polymorphic variant (rs6265) in the BDNF gene increases the likelihood of developing MDD in the Malaysian population by approximately 2.05 times	[32]
Elder people; n=110	The Met / Met variant of the rs6265 polymorphism of the BDNF gene affects the pathogenesis of geriatric depression	[33]
Elder people; n=398	Carriers of the Met66 allele in the BDNF gene are almost twice as likely to develop geriatric depression as those of the Val66 allele.	[34]
Mexican-Americans; n=284	The G / G variant of the rs6265 polymorphism of the BDNF gene is associated with major depressive disorders in Mexican Americans.	[35]
Dead people (37 suicides died)	Carrier of the Met allele of the rs6265 polymorphism of the BDNF gene has been associated with the occurrence of MDD and with suicide.	[36]
Adolescents from 12 to 17 years of age; n = 246	no relationship was found between the rs6265 polymorphism of the BDNF gene and MDD in the Mexican youth population,	[37]
Schizophrenia patients in the Chinese Han population; n = 456	The Val66Met variant of the rs6265 polymorphism of the BDNF gene is an important factor in the severity of anxiety/depression symptoms in patients with schizophrenia.	[38]
Patients with the acute coronary syndrome; n = 378	There is a relationship between the rs6265 polymorphism of the BDNF gene and the risk and response to depression treatment in acute coronary syndrome. BDNF may therefore act as a depression biomarker in acute coronary syndrome.	[39]

concerning the relationship of the BDNF Val66Met gene variant with MDD.

As can be seen in the attached Table 1, there is no consensus among studies of the rs6265 genetic variant of the BDNF gene and its relationship to the occurrence of MDD. Inconsistencies in the association studies of the Val66Met polymorphism of the BDNF gene with mood disorders may also be due to a lack of statistical power in small sample sizes and from differences between studies in inclusion criteria such as the definition of the MDD phenotype or ethnicity. Another problem contributing to the inconsistency in the relationship between the rs6265 polymorphism of the BDNF gene and MDD is the difference between the sexes in the prevalence of MDD is the gender difference in the etiology of MDD. Further research on the linkage of the BDNF gene to MDD needs to be carried out, and it must be conducted in a variety of populations and sample sizes to understand the role of BDNF and the different mechanisms in the etiology of MDD [31,40].

The conducted meta-analyses examining the relationship of Val66Met with MDD also do not provide clear answers. Gyekis et al. carried out a meta-analysis of 26 studies. The meta-analysis did not identify the relationship between the rs6265 polymorphism of the BDNF gene and MDD [41]. Studies by Pei et al. include five studies involving 523 cases with geriatric depression. Meta-analysis showed that the Met variant of the rs6265 polymorphism of the BDNF gene is related to MDD [45]. The meta-analysis of Verhagen et al. involved 14 studies including 2,812 cases of MDD, Asian and Caucasian. The Met variant of the rs6265 polymorphism of the BDNF gene is of greater importance in the development of MDD in men than in women [46].

5.1.2 SNP rs6265 in addictions

Substance dependence is a neuropsychiatric disorder characterized by a recurrent desire to continue taking medication despite harmful consequences [44]. It is a multifactorial syndrome involving a complex interaction between genes and the environment. The data suggest that the underlying mechanisms regulating these persistent behavioral abnormalities include changes in gene expression in the brain's reward circuits, particularly in the mesolimbic dopaminergic system. Over the past decade, research using genome-wide association studies has identified genes potentially involved in the risk of addiction to psychoactive substances. These studies also demonstrated the key role of epigenetic mechanisms in mediating the lasting effects of drug abuse on the brain in animal models of addiction. Interactions between environmental and genetic risk factors have also been shown to contribute to the emergence and development of addiction, as environmental risk factors tend to have a greater impact on children with genetic susceptibility. Thus, given the relationship between genetics and the environment, epigenetics may play a key role in the pathogenesis of addiction [45]. Of the 275 million users

Table 2. Relationship of the rs6265 polymorphism of the BDNF gene and addiction in different populations.

Study group	Addictive substance	Results	References
Thai men; n = 200	nicotine	Cigarette smoking may be one of the determinants of serum BDNF levels, but the rs6265 polymorphism of the BDNF gene probably does not influence smoking tendency among Thai men.	[49]
Chinese men; n = 136	nicotine	The rs6265 polymorphism of the BDNF gene may not be related to smoking susceptibility in the Chinese male population, but carriers of the Met / Met allele rs6265 polymorphism of the BDNF gene started smoking at an earlier age.	[50]
Teenagers; n = 530	alcohol	Carriers of the Met rs6265 polymorphism of the BD gene with well-being values of multiple collections leaned towards alcohol and drank alcohol.	[51]
Chinese methamphetamine abusers; n = 138	methamphetamine	The results of the research suggest that the Val / Val variant of the rs6265 polymorphism of the BDNF gene may affect attention impulsiveness in people who abuse methamphetamine. In addition, this polymorphism may contribute to the age of initiation of methamphetamine use.	[52]
German nationals; n = 203	nicotine	No association was found between smoking and the rs6265 polymorphism of the BDNF gene.	[53]
Patients from addiction treatment programs in Poland; n = 154	alcohol	The Val / Val variant in the Val66Met polymorphism is associated with a higher risk and earlier relapse in patients treated for alcohol dependence.	[54]
Heroin addiction patients; n = 96	heroin	The rs6265 polymorphism of the BDNF gene influences the age of onset of heroin abuse. People with the Val66Met variant of the rs6265 polymorphism of the BDNF gene suffer from addiction earlier.	[55]
Thai men; n = 100	methamphetamine	The rs6265 polymorphism of the BDNF gene is associated with methamphetamine dependence in the Thai population, with the G / G genotype being more common in methamphetamine-dependent individuals but reducing the onset of methamphetamine-dependent psychosis.	[56]
Caucasian patients of Croatian origin; n = 675	alcohol	The rs6265 polymorphism of the BDNF gene does not correlate with specific alcohol-related phenotypes in ethnically homogeneous non-drug users and alcohol addicts.	[57]
Heroin-dependent patients in the Chinese population; n = 486	heroin	The rs6265 polymorphism of the BDNF gene may have an impact on the age of onset of heroin dependence in the Chinese population.	[58]
Patients in depression related to alcohol dependence (AD-D); n = 166	alcohol	The rs6265 polymorphism of the BDNF gene is associated with the appearance of depression associated with alcohol dependence.	[59]

of any drug in the last year, it is estimated that around 36.3 million, or almost 13 percent, suffer from drug use disorders [46].

Currently, psychoactive substances used in Europe constitute a more diverse group than they used to be. It is becoming more and more common to take different substances at the same time [47].

Substance dependence is characterized by at least three phases: 1) continuation of substance use despite adverse consequences; 2) the effectiveness of the substance decreasing with time or the necessity to use higher doses to obtain the same desired effect (tolerance); 3) physical and mental symptoms of stress, discomfort, or impairment after restriction or cessation of substance use (withdrawal). These three phases of addiction are related to structural and functional changes in the brain that can be collectively explained as neuronal plasticity. Permanent changes in synapse strength underlie neural plasticity, and these changes are necessary for the efficient storage of information and the formation of memory. These synaptic changes are critical to the body's adaptive responses underpinning various behavioral modifications, including drug addiction, and are facilitated by increased synthesis and release of Brain-derived neurotrophic factor (BDNF) [48]. Table 2. presents an overview of publications concerning the relationship between the BDNF Val66Met gene variant and the occurrence of addictions.

As can be seen in the attached table 2, the results in terms of the participation of the rs6265 polymorphism of the BDNF gene in addictions are inconclusive. Therefore, more studies in different populations are needed to determine how these variants affect gene expression and function [60].

5.1.3. SNP rs6265in sport

Several environmental and genetic factors affect human fitness [61]. BDNF is known to regulate neuronal survival, growth, neurogenesis, and synaptic plasticity, and the BDNI rs6265 polymorphism is related to serum BDNF concentration in response to exercise [62]. This SNP may likely affect neuronal adaptation and thus the ability to activate the appropriate muscles and generate more power when performing jumps and sprints [63]. The rs6265 polymorphism of the BDNF gene influences the psychological stress response as well as exercise motivation. In particular, this has a clear impact on the positive/negative thinking of the individual during the competition. In this way, the athlete can be better and more effectively guided to better manage their emotions and stress to achieve optimal results [64]. Table 3. presents an overview of publications regarding the relationship of the BDNF Val66Met gene variant with athlete status.

Table 3. Relationship of the rs6265 polymorphism of the BDNF gene and achievements in sport

Study group	Results	References
Elite male youth soccer players from Uruguay; n = 535	BDNF (rs6265) CC homozygotes showed greater horizontal power, acceleration, and sprint	[63]
Healthy male volunteers who underwent intense aerobic training on a treadmill three times a week for 4 months; n = 221	The Val / Val variant of the rs6265 polymorphism of the BDNF gene weakens the reactivity of blood vessels and the serum BDNF response to exercise training, and such a response is associated with serum BDNF concentrations in healthy individuals.	[65]
Judo athletes; n = 74	The Met /Met variant of the rs6265 polymorphism of the BDNF gene is associated with susceptibility to stress. The incidence of this polymorphism in judo athletes was lower, suggesting that judo athletes have greater stress resistance.	[66]
Swimmers; n = 105	Performance swimmers have a higher frequency of the Val / Met variant of the rs6265 polymorphism in the BDNF gene, suggesting that they are better at controlling and learning motor skills.	[66]
Australian Rules Football (ARF); n=30	The A / A and A / G variants of the rs6265 polymorphism of the BDNF gene are predictors of both total kicks and handballs in the ARF game.	[67]
Young, healthy participants with no known neurological disorders; n = 32	The rs6265 polymorphism of the BDNF gene is not functionally significant for the effect of acute aerobic exercise on motor learning	[68]

Summary

Brain-derived neurotrophic factor (BDNF), the most abundant of the neurotrophins in the brain, is recognized as playing an important role in the survival, differentiation, and outgrowth of select peripheral and central neurons during development and in adulthood. It is well known that BDNF participates in use-dependent plasticity mechanisms such as long-term potentiation, learning, and memory. Since rs6265 polymorphism in the BDNF was first described by Egan et al. [28], it has become a frequently studied genetic variant in various diseases. SNP rs6265 producing a valine to methionine substitution in the proBDNF at codon 66, affects the intracellular trafficking and activity-dependent secretion of BDNF. Furthermore, this SNP is related to hippocampal volume and hippocampus-mediated memory performance in humans [69].

Few studies are investigating the relationship between rs6265 polymorphism and predisposition to play sports. Further research is needed on numerous groups of athletes to determine the biological role of BDNF polymorphism in the predisposition to play sports. The results on the effect of rs6265 BDNF polymorphic variants on the risk of MDD and addition are inconsistent, indicating a significant association in some studies and none in others. It is probably related to genotypic and phenotypic heterogeneity in different studied populations [70,71]. Therefore, more studies are needed to determine how rs6265 affects gene expression and function.

Conflict of interest

The author has declared no conflict of interest.

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