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DRD1 and DRD4 dopamine receptors in the etiology of preeclampsia

Receptory dopaminy DRD1 oraz DRD4 w etiologii stanu przedrzucawkowego

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Abstract

Introduction: *Recent reports have suggested an association between genetic polymorphisms of dopamine receptors and the development of an increased risk of chronic hypertension, as well as preeclampsia (PE).*

Objectives: *The aim of the study was to evaluate the impact of the -48A>G DRD1 and -521C>T DRD4 polymorphisms in the etiology of PE among Polish women.*

Material and methods: *Ninety-eight preeclamptic women and 120 healthy pregnant controls were enrolled in the study. The investigated polymorphisms of the DRD1 and DRD4 genes were identified using PCR/RFLP methods.*

Results: *As far as the -48A>G DRD1 polymorphism is concerned, the mutated -48GG genotype was more often found in controls (14.2%) than in the PE group (10.2%, ns), and the subgroup with severe PE (8.2%). Also, the frequency of the mutated -48G allele was higher in controls (39.6%) than in the PE group (33.2%, ns), and in the subgroup with severe PE (31.6%, ns). As for the -521C>T DRD4 polymorphism, a similar occurrence of the mutated -521TT genotype and the -521T allele in all of the investigate groups was observed. Lower serum concentrations of total protein (5.59 g/L and 5.57 g/L vs. 6.17 g/L in carriers of the -521CC genotype, p=0.02) were noted in patients with the mutated homozygous -521TT genotype and heterozygous -521CT genotype of DRD4.*

Conclusions: *The obtained results suggest a possible protective role of the mutated -48G DRD1 allele in the etiology of preeclampsia, especially its severe form. The presence of the mutated -521T DRD4 allele could influence the decrease of total blood protein in preeclamptic patients. The observed frequency of dopamine DRD1 and DRD4 polymorphisms is similar to the distribution of these variants in other Caucasian populations.*

Key words: **dopamine receptor DRD1** / **dopamine receptor DRD4** / **preeclampsia** / / **genetic polymorphism** /

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Streszczenie

Wstęp: *W ostatnich latach sugeruje się związek polimorfizmów genów receptorów dopaminy z rozwojem nadciśnienia tętniczego przewlekłego, jak również stanu przedrzucawkowego.*

Cel pracy: *Celem pracy była ocena udziału polimorfizmów -48A>G genu receptora DRD1 oraz -521C>T genu DRD4 w etiologii stanu przedrzucawkowego w populacji kobiet polskich.*

Materiał i metody: *Do badania włączono 98 ciężarnych ze stanem przedrzucawkowym oraz 120 zdrowych ciężarnych. Badane polimorfizmy genów DRD1 oraz DRD4 oznaczano metodą reakcji łańcuchowej polimerazy oraz polimorfizmu długości fragmentów restrykcyjnych (PCR/RFLP).*

Wyniki: *W zakresie polimorfizmu DRD1 genotyp zmutowany -48GG częściej występował w grupie kontrolnej (14.2%) w porównaniu do grupy z PE (10.2%, ns) oraz podgrupy z ciężką postacią PE (8.2%, ns). Również częstość występowania zmutowanego allela -48G była większa w grupie kontrolnej (39.6%) w porównaniu do grupy z PE (33.2%, ns) oraz podgrupy z ciężką postacią PE (31.6%). Dla polimorfizmu -521C>T genu DRD4 wskazano podobną częstość występowania zmutowanego genotypu -521TT oraz allela -521T we wszystkich badanych grupach kobiet. U pacjentek z PE nosicielek genotypu homozygotycznego zmutowanego -521TT i genotypu heterozygotycznego -521CT obserwowano niższe stężenia białka całkowitego w surowicy (odpowiednio 5.59 g/L i 5.57 g/L) w porównaniu do nosicielek genotypu -521CC (6.17 g/L) (p=0.02).*

Wnioski: *Wyniki pracy sugerują możliwy ochronny udział zmutowanego allela -48G DRD1 w patogenezie ciężkiej postaci stanu przedrzucawkowego. Obecność zmutowanego allela -521T DRD4 może wpływać na obniżenie wartości białka w surowicy krwi u kobiet ze stanem przedrzucawkowym. Obserwowana częstość występowania genotypów i alleli polimorfizmów receptorów DRD1 oraz DRD4 jest podobna do rozkładu tych wariantów w innych populacjach rasy kaukaskiej.*

Słowa kluczowe: **receptor dopaminy DRD1** / **receptor dopaminy DRD4** / / **stan przedrzucawkowy** / **polimorfizm genetyczny** /

Introduction

Preeclampsia (PE) is common complication in pregnancy, affecting about 5-10% of all pregnant women [1]. Moreover, the disease is the cause of increased risk of maternal, fetal, and neonatal morbidity and mortality. Despite extensive research, the exact etiology of PE remains unclear. One of the reasons of PE development could be the disturbances of enzyme and receptor activity involved in blood pressure regulation.

Dopamine is an important blood pressure regulator, acting directly with specific receptors located in vessel walls. Moreover, dopamine influences the kidney function and is involved in proper balance of fluids and electrolytes [2]. There are two groups of dopamine receptors: the D1 group (D1 and D5 receptors, which stimulate adenylyl cyclase) and the D2 group (D2, D3 and D4 receptors, which inhibit adenylyl cyclase) [3, 4, 5, 6]. These receptors are mainly located in blood vessels in kidneys, where synthesis and excretion of renin take place. D1 receptors may also act by interaction with renin-angiotensin system and sympathetic system. Co-action of the D1 receptor and protein G activates dopamine signaling pathway, which influences vessel dilatation, sodium hemostasis, and blood pressure [7, 8]. Failed D1 and D4 receptor activity may be directly correlated with the development of chronic arterial hypertension [2, 9]. Stimulation of the D1 receptor causes the natriuretic effect, which is impaired in patients with arterial hypertension [2, 10]. The D4 receptor is also found in heart muscle and central nervous system [11, 12].

The *DRD1* gene is located on chromosome 5 (5q35.1) (2 exons) [13], and the *DRD4* gene on chromosome 11p15.5 (4 exons) [14]. Few polymorphisms in the promoter region of these genes have been described [10, 15]. One of the reasons of failed protein receptor activity could be the presence of genetic polymorphisms. Involvement of these genetic variants has already been proven in the etiology of mental diseases, as well as alcohol and narcotic addiction [3, 6]. Studies including Caucasian and Asian populations have shown a possible correlation of genetic polymorphism of the *DRD1* and *DRD4* genes with chronic arterial hypertension [4, 10, 16].

It has been already suggested that carriers of the *DRD1* or *DRD4* gene polymorphisms are at an increased risk of chronic hypertension and preeclampsia. Lower number of DRD1 receptors in the umbilical artery results in an impaired tension of vessel walls [17]. Studies concerning the *DRD4* gene in patients with gestational hypertension revealed a significant correlation with the mutated *-521T* allele and the etiology of PE [18].

Table I. Hydrolysis fragments and restriction enzymes used in the analysis.

Polymorphism	Restriction enzyme (producer)	Sequence	PCR product	Hydrolysis fragments
DRD1 *-48A>G*	*HpyF3*I (*Dde*I) (ThermoScientific)	5'…C↓T N A G…3' 3'…G A N T↑C…5'	404 bp	*AA* (219 bp, 143 bp, 42 bp) *AG* (261 bp, 219 bp, 143 bp, 42 bp) *GG* (261 bp, 143 bp)
DRD4 *-521C>T*	*Nsb*I (*Fsp*I) (ThermoScientific)	5'…TGC↓GCA…3' 3'…ACG↑CGT…5'	285 bp	*CC* (285 bp) *CT* (285 bp, 176 bp, 109 bp) *TT* (176 bp, 109 bp)

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Objectives

The aim of the study was to evaluate the involvement of the *-48A>G DRD1* and the *-521C>T DRD2* gene polymorphisms in the etiology of PE among Polish women.

Material and methods

The study group consisted of 98 pregnant women with PE (mean age: 30.1±5.5 years, mean gestational age: 33.8±3.6 weeks, mean systolic and diastolic blood pressure: 171.1±21.1 mmHg and 106.2±13.8 mmHg, respectively), whereas 120 healthy pregnant women (mean age: 28.7±4.8 years, mean gestational age: 39.1±1.3 weeks, mean systolic and diastolic blood pressure: 108.3±11.2 mmHg and 67.3±8.6 mmHg, respectively) were recruited as controls. The patients were enrolled at the Division of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poland, between 2011-2014. All subjects gave their written informed consent to participate in the project. Local Ethics Committee approved of the study.

Preeclampsia was diagnosed according to the ACOG criteria (arterial blood pressure >140/90 mmHg, proteinuria >30mg/dL in urine sample). Chronic hypertension, cardio-vascular diseases, nephropathy, diabetes mellitus, multiple gestation, and non-Caucasian race constituted the exclusion criteria.

Genomic DNA was extracted from blood leucocytes using QIAamp DNA Blood Mini Kit (QIAGEN Inc., Germany). Genotyping was performed using the polymerase chain reaction (PCR) and restriction length fragment polymorphism (RLFP) procedures. For the *-48A>G DRD1* polymorphism, the following starters were used for amplification: F: 5'-GGC TTT CTG GTG CCC AAG ACA GTG-3' and R: 5'-AGC ACA GAC CAG CGT GTT CCC CA-3'[Sato et al. 2000]. For the *-521C>T DRD1* polymorphism, the following starters were used: F: 5'- CGG GGG CTG ACC ACC AGA GGC TGC -3' and R: 5'- GCA TCG ACG CCA GCG CCA TCC TAC -3' [19]. Restrictive enzymes, obtained PCR products and restriction fragments are presented in Table I.

Statistical analyses were performed with SPSS 22.0 PL for Windows. The *p* value of <0.05 was considered as statistically significant. Frequencies of genotypes were compared by chi-square test (one-sided Fisher test) and Fisher Exact Probability Test. The expected genotype frequencies were calculated from allele frequencies with the use of the Hardy-Weinberg equation.

Results

Clinical data and laboratory parameters were analyzed in both groups. Mean body mass before pregnancy was 66.8±17.5 kg and 60.3±9.4 kg in the PE group and the control group, respectively (p=0.004). Mean body mass at the end of pregnancy was 81.8±16.9 kg and 75.3±10.5 kg in the PE group and controls, respectively (p=0.001). Mean platelet level was lower in the PE group as compared to controls (194.77±68.00 vs. 207.38±50.72 G/L, p=0.08). Higher level of proteinuria was observed in the PE group as compared to controls (302.04±191.60 vs. 15.81±9.16 mg/dL, p<0.0001) (Table II).

The frequency of the heterozygotic *-48AG* genotype was lower in the PE group (45.9%) as compared to controls (50.8%, OR=0.82, ns). Also, the mutated *-48GG* genotype was lower in the PE group (10.2%) than in controls (14.2%, OR=0.69, ns). The frequency of the mutated *-48G* allele was 33.2% and 39.6% in the PE group and controls, respectively (OR=0.76, ns). The same observation was noted in the group with severe PE. The mutated *-48GG* genotype was observed less often in the severe PE group as compared to controls (8.2 vs. 14.2%, OR=0.54, ns). Also, the frequency of the mutated *-48G* allele was lower in the severe PE group (31.6 vs. 39.6%, OR=0.71, ns) (Tables III and IV).

The mutated *-521TT* genotype was observed in similar frequency in both analyzed groups (35.7 *vs.* 33.3% in controls, OR=1.11, ns). There was a similar frequency of the mutated *-521T* allele in the PE group and controls (59.2 *vs.* 56.7%, OR=1.11, ns). Also, similar frequencies of the mutated *-521TT* genotype (30.6 *vs.* 33.3% in controls, OR=0.88, ns) and the mutated *-521T* allele (56.1 vs. 56.7% in controls, OR=0.98, ns) were noted in the subgroup with severe PE and in the control group (Tables V and VI).

Table II. Clinical data and laboratory parameters of women from the study and control groups.

	Study group n=98	Control group n=120	p
Height (cm) mean ± SD range median	 165.2±6.7 140-180 165	 167.4±4.9 150-180 168	0.011
Body mass before pregnancy (kg) mean ± SD range median	 66.8±17.5 42-150 64	 60.3±9.4 40-97 59,5	0.004
Body mass at the end of pregnancy (kg) mean ± SD range median	 81.8±16.9 50-157 78.25	 75.3±10.5 52-106 75	0.001
Hb (mmol/L) mean ± SD range median	 7.23±1.51 4.8-13.6 7.20	 6.72±0.79 4.5-8.8 6.77	0.003
Htk (L/L) mean ± SD range median	 0.33±0.04 0.23-0.43 0.34	 0.32±0.04 0.22-0.42 0.32	0.051
PLT (G/L) mean ± SD range median	 194.77 ± 68.00 47-352 198.00	 207.38 ± 50.72 114-314.6 206.95	0.080
Proteinuria mean ± SD range median	 302.04±191.60 75-500 225	 15.81±9.16 0-25 25	<0.0001
Nulliparous multiparous	59 (60.2%) 39 (39.8%)	67 (55.8%) 53 (44.2%)	0.300
Mode of delivery spontaneous vaginal cesarean section	 11 (11.2%) 87 (88.8%)	 103 (85.8%) 12 (10.0%)	<0.0001
Other deliveries (forceps, vacuum extractor)		5 (4.2%)	-

Table III. The frequency of genotypes and alleles of the -48A>G DRD1 gene polymorphism in the study and control groups.

-48A>G DRD1	*Study group PE (n=98)*		*Control group (n=120)*		*OR*	*95%CI*	*p*
Genotypes	*Observed value n(%)*	*Expected value (%)*	*Observed value n(%)*	*Expected value (%)*			
-48AA	43 (43.9)	44.7	42 (35.0)	36.5	1.45	0.84-2.51	0.12
-48AG	45 (45.9)	44.3	61 (50.8)	47.8	0.82	0.48-1.45	0.28
-48GG	10 (10.2)	11.0	17 (14.2)	15.7	0.69	0.30-1.58	0.25
Total	98 (100.0)	100.0	120 (100.0)	100.0			
Alleles							
-48A	131 (66.8)	-	145 (60.4)	-	1.32	0.89-1.96	0.10
-48G	65 (33.2)	-	95 (39.6)	-	0.76	0.51-1.12	0.10
Total	196 (100.0)		240 (100.0)				

Table IV. The frequency of genotypes and alleles of the -48A>G DRD1 gene polymorphism in the group with severe preeclampsia and the control group.

-48A>G DRD1	*Severe PE (n=49)*		*Control group (n=120)*		*OR*	*95%CI*	*p*
Genotypes	*Observed value n(%)*	*Expected value (%)*	*Observed value n(%)*	*Expected value (%)*			
-48AA	22 (44.9)	46.8	42 (35.0)	36.5	1.51	0.72-3.14	0.15
-48AG	23 (46.9)	43.2	61 (50.8)	47.8	0.86	0.41-1.76	0.38
-48GG	4 (8.2)	10.0	17 (14.2)	15.7	0.54	0.14-1.78	0.21
Total	49 (100.0)	100.0	120 (100.0)	100.0			
Alleles							
-48A	67 (68.4)	-	145 (60.4)	-	1.41	0.84-2.42	0.11
-48G	31 (31.6)	-	95 (39.6)	-	0.71	0.41-1.19	0.11
Total	98 (100.0)		240 (100.0)				

Clinical data and investigated polymorphisms

A tendency to lower systolic blood pressure in the carriers of the homozygotic genotype *-48AA* (167.4 mmHg in *-48AA* genotype vs. 173.0 mmHg in *-48GG* genotype vs. 174.1 mmHg in *-48AG* genotype, ns) was observed. Similar observations were made with regard to mean diastolic blood pressure values (104.1 mmHg in *-48AA* genotype vs. 108.0 mmHg in *-48AG* genotype vs. 107.5 mmHg in *-48GG* genotype, ns).

Among the preeclamptic women, the level of serum total protein was the highest in the subgroup with the *-521CC* genotype (6.17 g/L). Lower values were observed in the subgroups with the *-521CT* genotype (5.57 g/L) and the *-521TT* genotype (5.59 g/L, p=0.02).

Discussion

Preeclampsia is a multifactorial obstetric complication and it seems that genetic polymorphisms could play an important role in its etiology. Additionally, several of them might be used as markers of early PE development. Identification of such markers would make the diagnosis and prevention of PE much easier. Thus, numerous researches have focused their attention on the significance of genes and their polymorphic variants in the development of preeclampsia [20, 21, 22, 23].

Studies in different populations revealed a correlation between chronic hypertension and dopamine receptors polymorphisms. An analysis of Sato et al., included 131 patients with essential hypertension and 136 healthy controls from Japanese population. Their study found a higher frequency of the mutated *-48G DRD1* allele in hypertensive as compared to normotensive subjects. Additionally, hypertensive carriers of the *-48G* allele had higher diastolic blood pressure in comparison to the other genotypes [16]. Lu et al., analyzed the *-48A*>G polymorphism in White and African American populations. Their study showed that the mutated *-48G* allele is more frequent in White as compared to African Americans. Moreover, diastolic blood pressure was lower in the carriers of the mutated *-48G* allele than in patients with the *-48A* allele [7]. Additionally, the analysis performed among White Americans suggested that the *-94A DRD1* allele may be a marker of an increased risk of renal dysfunction [24].

The results of studies conducted among European populations are also conflicting. A study by Beige et al., performed in 493 hypertensive patients and 209 normotensive controls, found no correlation between *DRD1 -48A>G* and *-94G>A* polymorphisms and arterial hypertension [10]. Cipolletta et al., analyzed a possible correlation between *-48A>G DRD1* polymorphism

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Table V. The frequency of genotypes and alleles of the -521C>T DRD4 gene polymorphism in the study and control groups.

-521C>T DRD4	*Study group PE (n=98)*		*Control group (n=120)*		*OR*	*95%CI*	*p*
Genotypes	*Observed value n(%)*	*Expected value (%)*	*Observed value n(%)*	*Expected value (%)*			
-521CC	17 (17.4)	16.7	24 (20.0)	18.8	0.84	0.42-1.67	0.37
-521CT	46 (46.9)	48.3	56 (46.7)	49.1	1.01	0.59-1.72	0.54
-521TT	35 (35.7)	35.0	40 (33.3)	32.1	1.11	0.63-1.95	0.41
Total	98 (100.0)	100.0	120 (100.0)	100.0			
Alleles							
-521C	80 (40.8)	-	104 (43.3)	-	0.90	0.61-1.32	0.33
-521T	116 (59.2)	-	136 (56.7)	-	1.11	0.76-1.63	0.33
Total	196 (100.0)		240 (100.0)				

Table VI. The frequency of genotypes and alleles of the -521C>T DR41 gene polymorphism in the group with severe preeclampsia and controls.

-521C>T DRD4	*Severe PE (n=49)*		*Control group (n=120)*		*OR*	*95%CI*	*p*
Genotypes	*Observed value n(%)*	*Expected value (%)*	*Observed value n(%)*	*Expected value (%)*			
-521CC	9 (18.4)	19.3	24 (20.0)	18.8	0.90	0.34-2.23	0.49
-521CT	25 (51.0)	49.2	56 (46.7)	49.1	1.19	0.58-2.44	0.36
-521TT	15 (30.6)	31.5	40 (33.3)	32.1	0.88	0.39-1.89	0.44
Total	49 (100.0)	100.0	120 (100.0)	100.0			
Alleles							
-521C	43 (43.9)	-	104 (43.3)	-	1.02	0.62-1.68	0.51
-521T	55 (56.1)	-	136 (56.7)	-	0.98	0.59-1.61	0.51
Total	98 (100.0)		240 (100.0)				

and renal dysfunction in patients with chronic arterial hypertension in Italian population. Their results suggested that patients with the *-48AA* genotype are at an increased risk of renal failure [4]. In Turkish patients, higher blood pressure values were observed in the carriers of the mutated *-48GG* genotype and lower blood pressure in the carriers of the *-48AA* genotype [25].

The number of studies on the *-521C>T DRD4* polymorphism and its connection with preeclampsia are limited. Studies on mice model showed that DRD4 activity influences the increasing blood pressure [11]. Villancourt et al., showed that the amount of dopamine receptors in the placenta is lower in preeclamptic patients as compared to healthy pregnant women [26]. These dopamine expression fluctuations prove the significant influence of dopamine on placental function [18].

Korobochka et al., performed a prospective analysis of 50 families (patient and both parents), aiming to evaluate the significance of the *-521C>T DRD4* polymorphism in the development of preeclampsia. Their results showed a statistically significant correlation between the *-521C>T DRD4* polymorphism and the risk of PE development (p=0.019). Moreover, a statistically significant correlation between the mutated *-521T* allele and systolic blood pressure values (p=0.036) was demonstrated. The *-521C>T DRD4* polymorphism, which reduces transcription of the *DRD4* gene, seems to increase the risk of PE. Moreover, the authors of that study suggest that the mutated homozygotic *-521TT* genotype may be a marker of severe PE [18].

To the best of our knowledge, our study has been the first to investigate *DRD1* and *DRD4* gene polymorphisms and their role in the development of preeclampsia in Polish pregnant women. Genetic analysis revealed a possible involvement of the mutated *-48G DRD1* allele in the etiology of preeclampsia, especially in its severe form. Moreover, biochemical analysis proved that the mutated *-521TT DRD4* genotype may influence the decrease of total blood protein in preeclamptic patients. A statistically significant difference in total blood protein was revealed in patients from the PE group (6.2 g/L in *521CC* carriers and 5.6 g/L in *-521TT* carriers, p=0.02).

Comprehensive analysis of the available literature allows to conclude that DRD1 and DRD4 dopamine receptors could play a role in the etiology of chronic arterial hypertension and preeclampsia. Moreover, genetic polymorphisms which modify dopamine receptors activity could take part in the process of changing the susceptibility to those complications. Noteworthy, there are only a few studies concerning the correlation of these polymorphisms with arterial hypertension and preeclampsia, especially in Caucasian populations. Further studies, with larger sample sizes, are needed to clarify the exact influence of genetic variants of dopamine receptors on the development of PE.

Conclusions

The obtained results suggest a possible protective role of the mutated *-48G DRD1* allele in the development of preeclampsia, especially in its severe form.

The presence of the mutated *-521T DRD4* allele could influence the decrease of total blood protein in patients with preeclampsia.

The observed frequency of dopamine *DRD1* and *DRD4* polymorphisms is similar to the distribution of these variants in other Caucasian populations.

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