The association between polymorphisms of β-adrenoceptors and preeclampsia

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Purpose : The β-adrenoceptors are pharmacologically classified into β_1-, β_2- and β_3-adrenoceptor. The gene of each subtype has polymorphisms related to their function (β_1-adrenoceptor: Ser49Gly, β_2-adrenoceptor: Gln27Glu, β_3-adrenoceptor: Trp64Arg). The objectives of this study were to analyse the allelic and genotypic distribution of the representative polymorphism of β-adrenoceptors in preeclampsia and to investigate whether combined genotype of β-adrenoceptors may be associated with preeclampsia.
Methods : Blood samples were collected from a Korean population (159 preeclamptic pregnancies and 168 normotensive pregnancies). The β_1-, β_2- and β_3-adrenoceptor genotypes was determined using polymerase chain reaction-restriction fragment length polymorphism.
Results : There were no differences in allelic and genotypic distribution of β_1- and β_2-adrenoceptor polymorphisms between the two groups. However, the Arg allele of β_3-adrenoceptor polymorphism were more frequent in preecalmpsia than in controls (P<0.05, OR=1.57, 95% CI=1.01-2.46). Moreover, prevalence of genotype carrying heterozygote of β_3-adrenoceptor polymorphism was increased in preeclampsia compared with controls (P<0.05, OR 1.76, 95% CI 1.06-2.92). When combination of the three polymorphisms were evaluated, pregnancies with the particular combined genotype that is consisted of heterozygote of β_1-, β_3-adrenoceptor and wild homozygote of β_2-adrenoceptor (Ser/Gly, Gln/Gln, Trp/Arg), showed a significant increase in the risk of preeclampsia (P<0.05, OR=3.01, 95% CI 1.12-8.08).
Conclusion : A particular combined genotype (Ser/Gly, Gln/Gln, Trp/Arg) of - adrenoceptors was associated with the risk of preeclampsia.

Key words : β-adrenoceptor polymorphisms, Preeclampsia

Introduction

Preeclampsia is a toxemia of pregnancy that is characterized by proteinuria and hypertension and generally begins after 20 weeks of gestation. It affects 5% of pregnancies and is a major cause occurring maternal mortality and fetal morbidity[1)]. The mechanism for developing preeclampsia has remained unclear. However, poor placentation is known as one of the major causes. And it is induced by multiplex factors such as insulin resistance, obesity, in-

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flammation, and genetic factors[2-6]. Mechanisms inducing significant vasoconstriction observed in preeclampsia are also complex and partly understood. This vasoconstriction is induced by many factors including β-adrenoceptors [7].

β-adrenoceptors are expressed in many organ systems such as the cardiac, vascular, endocrine and central nervous system and play a key role in the regulation of bodily functions through binding with endogenous hormones. These have three different subtypes and are identified pharmacologically: β_1-, β_2- and β_3- adrenoceptor[8].

The β_1-adrenoceptor gene is encoded by an intron-less gene and is located on chromosome 10q24-26[9]. The human β_1-adrenoceptor has single nucleotide polymorphism (SNP) related to receptor function in the coding region. SNP is located at position 49 in the N-terminus where a serine is substituted by a glycine (Ser49Gly) and associated with the heart failure[10, 11]. The human β_2-adrenoceptor is also encoded by an intron-less gene located on chromosome 5q31-32[12]. The coding region of β_2-adrenoceptor gene has nine single base substitutions, but three of those have functional effects in vitro and in vivo[13]: Arg16Gly and Gln27Glu in the N-terminus and Thr64Ile in the first transmembrane spanning region. Among them, Gln27Glu is reported an association with the risk of hypertension in various studies[14, 15]. The human β_3-adrenoceptor gene is located on chromosome 8p11.1-8p12 and consisted of a large exon, an intron and a second exon[16]. It has one major SNP at codon 64 beginning the first intracellular loop of the β_3-adrenoceptor. And tryptophan is substituted by an arginine (Trp64Arg) at this SNP[17].

Two studies have recently reported that Trp64Arg of the β_3-adrenoceptor is not associated with preeclampsia[18, 19]. However, the correlation between polymorphisms of β_1 or β_2-adrenoceptor and preeclampsia is unknown. Moreover, the effect of combined polymorphisms of β-adrenoceptors has never been reported in cases of preeclampia. Therefore, we selected the most common three polymorphisms (β_1-adrenoceptor: Ser49Gly, β_2-adrenoceptor: Gln27Glu, β_3-adrenoceptor: Trp64Arg) influencing to the function of each β-adrenoceptor and analyzed each polymorphism of β-adrenoceptor in a group of preeclampia pregnancies and a group of normotensive pregnancies. The results were analysed to examine whether preeclampia affects the allelic and genotypic distribution of each β-adrenoceptor polymorphism and whether combined genotypes of the β-adrenoceptors are associated with preecalmpsia.

Materials and Methods

1. Subjects

We studied polymorphisms of the β-adrenoceptors in 327 pregnant women at Cheil General Hospital in Seoul, Korea. Women were divided in two groups: the case group consisted of 159 women who developed preeclampsia during their pregnancy and the control group consisted of 168 normotensive women who had a normal pregnancy outcome. All subjects had no history of preexisting hypertension, diabetes mellitus, liver disease, or chronic kidney disease. The Ethics Committee at Cheil General Hospital approved this study and written informed consent was obtained from all enrolled subjects.

Preeclampsia is defined as the new-onset of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) and proteinuria (≥300 mg in a 24 hr urine collection or one dipstick measurement of ≥1+) in woman after 20 weeks' gestation according to the Committee Terminology of the American College of Obstetricians and Gynecologists (ACOG)'s definition[20]. Study subjects were matched by race, gestational age at the time of blood sampling.

2. Genotyping procedures for β-adrenoceptor

Genomic DNA was extracted from peripheral blood using QIAamp DNA blood Mini kits (Qiagen, Valencia, CA). The polymerase chain reactionrestriction fragment length polymorphism assay (PCR-RFLP) was used for genotyping analysis. The polymorphic region of each β-adrenoceptor gene was amplified by PCR. Primers for PCR

are shown in Table 1.

For position 49 genotyping (Ser49Gly) in the β1-adrenoceptor gene, the PCR reaction solution (10 μL) contained 10 ng genomic DNA, 10 pM primer pair, 0.25 mM dNTP (containing deaza-7-GTP, Roche diagnostics, Mannheim, Germany), 1.5 mM $MgCl_2$, and 0.5 U polymerase of GC rich PCR system (Roche diagnostics, Mannheim, Germany). PCR conditions included predenaturation at 95 oC for 5 min, 35 cycles of 95℃ for 30 sec, 56℃ for 30 sec, 72℃ for 60 sec, and final extension at 72℃ for 10 min.

For position 27 genotyping (Gln27Glu) in the β_2-adrenoceptor gene and position 64 genotyping (Trp64Arg) in the β_3-adrenoceptor gene, the 10 μL PCR mixture contained 10 ng genomic DNA, 1 X PCR reaction buffer, 1.5 mM $MgCl_2$, 0.25 mM dNTP, 10 pM primer pair, and 0.5 U Taq Polymerase. Temperature cycling conditions were 94℃ for 5 min, 35 cycles of 94℃ for 30 sec, 63℃ for 30 sec, 72℃ for 30 sec, and 72℃ for 5 min.

PCR products (5 μL) were added to 1 X restriction enzyme buffer containing bovine serum albumin and 0.25 U of restriction enzyme. The final reaction volume was adjusted to 10 μL with deionized water. These mixtures were incubated at conditions suitable for the action of restriction enzymes. The treatment condition of the restriction enzyme is shown in Table 1. After restriction enzyme digestion, digestion products were run on a 3% nusieve agarose gel containing ethidium bromide and visualized using a Molecular Imager FX (Bio-Rad Laboratories Pty Ltd., Hercules, California, USA). For quality assurance, ten percent of the samples were analysed three times and all genotypes were confirmed by two independent observers.

Restriction digestion was used to distinguish alleles at each position of polymorphism. In Ser49Gly of the β_1-adrenoceptor gene, the Ser allele remained the PCR product with 420 base pairs (bp), while the Gly allele containing an Eco0109I restriction site resulted in fragments of 312 bp and 108 bp. In Gln27Glu of the β_2-adrenoceptor gene, the Gln allele produced three bands by BbvI restriction enzyme: a 260 bp, 65 bp, and 55 bp fragments. However, the Glu allele that lost a cut site of enzyme produced fragments of 315 bp and 65 bp. In Trp64Arg of the β_3-adrenoceptor gene, BstN1 digested the cut sites of the Trp allele to produce fragments of 97 bp, 64 bp, 61 bp and 33 bp, while the Arg allele was not cut by BstN1 and resulted in fragments of 158 bp, 64 bp and 33 bp.

3. Statistical analysis

Assuming that the frequency of the rare allele would be 10% in the controls and 20% in cases and that the ratio of numbers of each group would be 1:1, our sample size had at least 80% power and error 0.05 by post hoc power analysis. Values of variables were expressed as mean standard deviation. A comparison of variables between two groups was performed using Mann-Whitney U test. Pearson's chi-square test and Fishers exact test were used to test for associations between preeclampsia and allele or genotype, odds ratio, and 95% confidence intervals. A *P*-value of less than .05 was considered statistically significant. Statistical analysis was performed with SPSS 12.0 statistical software.

Table 1. The PCR Primer Sequence and Condition of Restriction Fragment Length Polymorphism (RFLP) for Genotyping Analysis of β_1-, β_2- and β_3-Adrenoceptor (AR)

Target	Primer sequences	RFLP condition
β_1-AR (Ser49Gly)	Forward: 5'-AGCCCGGTAACCTGTCGT-3'	Eco109I
	Reverse: 5'-TGACACACAGGGTCTCGATG-3'	(56℃, 2 hr)
β_2-AR (Gln27Glu)	Forward: 5'-CAGCCAGTGCGCTTACCTGC-3'	Bbv1
	Reverse: 5'- CACAGCACATCAATGGAAGTC -3'	(37℃, 2 hr)
β_3-AR (Trp64Arg)	Forward: 5'-GCGCCCAATACCGCCAACAC-3'	BstN1
	Reverse: 5'- CCACCAGGAGTCCCATCACC-3'	(56℃, 2 hr)

Results

Clinical characteristics of the women with preeclampsia (PE) and the healthy pregnant women (control) are shown on Table 2. Between the two groups, there were significant differences in blood pressure, gestational age at delivery, and birth weight of the baby (P<0.001). Proteinuria was found only in PE.

The genotypes and allele frequencies of the two groups are presented in Table 3. In the genotype of the β_1-adrenoceptor, the frequencies of wild homozygote (Ser/Ser) and heterozygote (Ser/Gly) were 69.2% and 30.2%, respectively, in the PE and 78.0% and 22.0%, respectively, in controls. There was no significant difference between the two groups in the genotype of the β_1-adrenoceptor. Frequencies of the wild allele (Ser) and variant allele (Gly) in β_1-adrenoceptor of the PE group (0.84 and 0.16, respectively) were also not different when compared with the control group (0.89 and 0.11, respectively) (Table. 3A). In genotypic and allelic frequencies of the β_2-adrenoceptor, no difference was found between the two groups (Table. 3B). However, in genotype and allelic frequency of the β_3-adrenoceptor, a statistically significant difference was

Table 2. Clinical Characteristics of the Preecalmpsia (PE) and Control (C)

Characteristics	Mean±SD		*P* value
	PE (N=159)	C (N=168)	
Age (years)	30.9±3.9	31.7±2.5	0.678
Systolic Blood Pressure (mmHg)	159.1±16.5	124.2±8.9	<0.001*
Diastolic Blood Pressure (mmHg)	100.7±11.9	77.5±7.6	<0.001*
Gestational age at delivery (weeks)	36.5±3.3	39.3±1.2	<0.001*
Birth weight of the offspring (g)	2613.6±802.6	3328.8±504.3	<0.001*
Proteinuria (dipstick results)	2.6±1.1	-	-

*significant difference. Abbreviation : N, number

Table 3. Genotype and Allele Frequencies in of β_1-, β_2- and β_3-Adrenoceptor (AR) in Control (C:N=168) and Preeclampsia (PE:N=159)

	Genotype			Alleles	
A. β_1-AR	Ser/Ser	Ser/Gly	Gly/Gly	Ser	Gly
	N (%)	N (%)	N (%)	N (F)	N (F)
C	131 (78.0)	37 (22.0)	0 (0.0)	299 (0.89)	37 (0.11)
PE	110 (69.2)	48 (30.2)	1 (0.6)	268 (0.84)	50 (0.16)
P value	-	0.09	0.46	-	0.08
OR (95% CI)	1.0 referent	1.54 (0.94-2.54)	-	1.0 referent	1.51 (1.96-2.38)
B. β_2-AR	Gln/Gln	Gln/Glu	Glu/Glu	Gln	Glu
	N (%)	N (%)	N (%)	N (F)	N (F)
C	116 (69.1)	49 (29.2)	3 (1.7)	281 (0.84)	55 (0.16)
PE	122 (76.7)	36 (22.6)	1 (0.6)	280 (0.88)	38 (0.12)
P value	-	0.16	0.36	-	0.11
OR (95% CI)	1.0 referent	0.70 (0.42-1.15)	0.32 (0.03-3.09)	1.0 referent	0.69 (0.44-1.08)
C. β_3-AR	Trp/Trp	Trp/Arg	Arg/Arg	Trp	Arg
	N (%)	N (%)	N (%)	N (F)	N (F)
C	132 (78.6)	34 (20.2)	2 (1.2)	298 (0.89)	38 (0.11)
PE	108 (67.9)	49 (30.8)	2 (1.3)	265 (0.83)	53 (0.17)
P value	-	0.03*	1.0	-	0.05*
OR (95% CI)	1.0 referent	1.76 (1.06-2.92)	1.22 (0.17-8.82)	1.0 referent	1.57 (1.01-2.46)

*significant difference, Abbreviations : N, number; F, frequency; OR, odds ratio; CI, confidence intervals

between the PE and control groups. The frequencies of wild homozygote (Trp/Trp) and heterozygote (Trp/Arg) were 67.9% and 30.8%, respectively, in PE and 78.6% and 20.2 %, respectively, in controls (P<0.05, OR=1.76, 95% CI 1.06 -2.92). Thus, the variant allele (Arg) of the β_3-adrenoceptor in the PE was more frequent than in the controls (P< 0.05, OR=1.57, 95% CI 1.01-2.46). However, the frequency of variant homozygote (Arg/Arg) was not different between the two groups (Table 3C).

We also considered whether combined genotypes of the three polymorphisms were associated with preeclampsia. According to genotype combinations, PE and controls were divided into 14 groups. Distributions of combined genotypes are presented in Table 4. The frequencies of combined genotype with wild homozygote of all polymorphisms (Ser /Ser,Gln/Gln,Trp/Trp) was 41.5% and 41.7% in PE and controls, respectively, and were not different in PE and controls. However, the frequencies of Ser/Ser,Gln/Glu,Trp/ Trp among single heterozygous groups was lower in PE than in controls and significantly different between the two groups (P=0.005) (Table 4). And pregnancies with Ser/ Ser,Gln/Glu,Trp/Trp showed resistance to risk of preeclampsia (OR=0.45, 95% CI 0.22-0.92) (Table 5). In particularly, the frequencies of Ser/Gly,Gln/Gln,Trp/Arg among double heterozygous groups presented more frequently in PE than in controls and showed significantly difference between the two groups (P=0.01) (Table 4). Moreover, pregnancies with Ser/Gly,Gln/Gln,Trp/Arg increased about 3 fold in risk of PE (OR=3.01, 95% CI 1.12-8.08) (Table 5). A combined genotype with heterozygote of all polymorphisms (Ser/Gly,Gln/Glu,Trp/Arg) did not resulted in any differences between the two groups. And a combined ge-

Table 4. Combined Genotypes of β_1-, β_2- and β_3-Adrenoceptor Polymorphism in Control (C) and Preeclampsia (PE)

Triplotype (β1, β2, β3)	Nature of genotype	PE		C		*P* value
		N	%	N	%	
Ser/Ser,Gln/Gln,Trp/Trp	Homo	66	41.5	70	41.7	NS
Ser/Ser,Glu/Glu,Trp/Trp	Homo	1	0.6	2	1.2	NS
Ser/Ser,Gln/Gln,Arg/Arg	Homo	1	0.6	1	0.6	NS
Ser/Ser,Gln/Gln,Trp/Arg	Single Hetero	15	9.4	18	10.7	NS
Ser/Ser,Glu/Glu,Trp/Arg	Single Hetero	0	0.0	1	0.6	NS
Ser/Ser,Gln/Glu,Trp/Trp	Single Hetero	14	8.8	33	19.6	0.005*
Ser/Ser,Gln/Glu,Arg/Arg	Single Hetero	1	0.6	0	0.0	NS
Ser/Gly,Gln/Gln,Trp/Trp	Single Hetero	23	14.5	21	12.5	NS
Ser/Gly,Gln/Gln,Arg/Arg	Single Hetero	0	0.0	1	0.6	NS
Ser/Gly,Gln/Glu,Trp/Trp	Double Hetero	4	2.5	6	3.6	NS
Ser/Gly,Gln/Gln,Trp/Arg	Double Hetero	17	10.7	6	3.6	0.01*
Ser/Ser,Gln/Glu,Trp/Arg	Double Hetero	12	7.5	6	3.6	NS
Gly/Gly,Gln/Glu,Trp/Arg	Double Hetero	1	0.6	0	0.0	NS
Ser/Gly,Gln/Glu,Trp/Arg	Triple Hetero	4	2.5	3	1.8	NS
		159	100	168	100	

*significant difference. Abbreviations : NS, non-significant difference; Homo, homozygote; Hetero, heterozygote

Table 5. Association between Particular Combined Genotypes of β_1-, β_2- and β_3-Adrenoceptor and Risk of Preeclampsia

Triplotype (β_1, β_2, β_3)	PE		C		OR (95% CI)	*P* value
	N	%	N	%		
Ser/Ser,Gln/Gln,Trp/Trp	66	41.5	70	41.7	1.0	-
Ser/Ser,Gln/Glu,Trp/Trp	14	8.8	33	19.6	0.45 (0.22-0.92)	0.03*
Ser/Gly,Gln/Gln,Trp/Arg	17	10.7	6	3.6	3.01 (1.12-8.08)	0.02*

*significant difference. Abbreviations : OR, odds ratio; CI, confidence intervals

notype with variant homozygote of all polymorphisms (Gly /Gly, Glu/Glu, Arg/Arg) did not detect in both groups.

Discussion

β-adrenoceptors, members of the GTP binding protein coupled receptor family with seven transmembrane regions, are key players in triggering β-adrenoceptor-mediated functions in many cell types throughout the body[21, 22]. Three subtypes of β-adrenoceptor are coupled to the Gs-protein and cAMP. These play a central role in the regulation of the effect of endogenous catecholamines, such as adrenaline and noradrenaline. These have functionally important polymorphisms. Among these polymorphisms, we selected three representative polymorphisms of β-adrenoceptors (β_1-adrenoceptor: Ser49Gly, β_2-adrenoceptor: Gln27Glu, β_3-adrenoceptor: Trp64Arg), previously examined in various races and populations with cardiac vascular disorders or obesity[23-29].

This study was to examine genotypes and allelic frequencies of the most common polymorphisms of three β-adrenoceptor subtypes in preeclampsia. And this was the first study to demonstrate an association between combined genotypes of β-adrenoceptors and preeclampsia.

In genotypes and allelic distributions of polymorphisms, the variant allele and heterozygote of the β_3-adrenoceptor polymorphism showed a statistically difference between PE and control groups. However,

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한글요약

목 적: 아드레너직 수용체는 약물학적 분류에 의해 β_1-, β_2-, β_3 아드레너직 수용체로 구분된다. 각 아류형 수용체의 유전자는 수용체의 기능에 영향을 주는 다형성들을 가진다(1 아드레너직 수용체: Ser49Gly, β_2 아드레너직 수용체: Gln27Glu,β_3 아드레너직 수용체: Trp64Arg). 이번 연구의 목적은 자간전증에서 아드레너직 수용체 아류형 각각의 대립 유전자와 유전자형의 분포를 연구하고, β 아드레너직 수용체들의 조합된 유전자형이 자간전증과 관계가 있는지 조사하는 것이다.

방 법: 한국인 자간전증 임산부 159명과 정상 임산부 168명으로부터 DNA 추출을 위해 혈액 샘플을 수집하였다. 각 아류형 수용체들의 유전자형은 중합효소 연쇄반응과 제한효소 절단 절편의 길이 다양성에 기초한 유전자 검색법을 사용하여 결정하였다.

결 과: β_1과 β_2 아드레너직 수용체 유전자의 다형성 연구에서, 각 수용체 유전자들의 대립 유전자와 유전자형 분포는 두 군 간에 차이가 없었다. 그러나 β_3 아드레너직 수용체 유전자의 돌연변이 대립유전자는 정상군보다 자간전증군에서 보다 빈번하게 나타났다(P<0.05, 위험도 1.57, 95% 신뢰구간 1.01-2.46). 더욱이 β_3 아드레너직 수용체 유전자의 이형접합체는 정상군과 비교했을 때 자간전증군에서 증가하였다(P<0.05, 위험도 1.76, 95% 신뢰구간 1.06-2.92). 아류형 아드레너직 수용체들의 세 가지 다형성들을 조합하여 평가하였을 때, β_1과 β_3 아드레너직 수용체는 이형접합체이고 β_2 아드레너직 수용체는 정상 동형접합체로 구성된 특별한 유전자형을 지닌 임산부는 자간전증의 위험이 유의성 있게 증가하였다(P<0.05, 위험도 3.01, 95% 신뢰구간 1.12-8.08).

결 론: 아류형 아드레너직 수용체들의 조합된 유전자형(Ser/Gly, Gln/Gln, Trp/Arg)은 자간전증의 위험과 관계가 있었다.

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