Archives of Medical Research 48 (2017) 180–186

ORIGINAL ARTICLE

Catechol-O-methyltransferase Gene Polymorphism (Val158Met) and Development of Pre-eclampsia

Ali Taravati,[a] Fatemeh Tohidi,[b] Mehrnaz Moniri,[a] and Kasra Kamali[a]

[a]*Department of Molecular and Cell Biology, Faculty of Basic Sciences, University of Mazandaran, Babolsar, Iran*
[b]*Department of Microbiology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran*

Received for publication August 14, 2016; accepted February 9, 2017 (ARCMED-D-16-00483).

Objectives. Catechol-O-methyltransferase (COMT) is a key enzyme in degradation pathways of estrogens and catecholamines. The present meta-analysis was done to elucidate the association of COMT Val158Met polymorphism with pre-eclampsia among pregnant women.

Methods. A literature search was conducted in electronic databases including PubMed, Scopus, Elsevier, Springer and Google Scholar to find eligible studies. The pooled odds ratios (ORs) with 95% confidence intervals were calculated under dominant, recessive, co-dominant, and allelic models.

Results. This meta-analysis included 6 eligible studies consisting 2596 cases and 4223 controls. The ORs for the COMT G472A polymorphism and pre-eclampsia were indicative of positive association under several genetic models. The results indicated that COMT Val158Met polymorphism was significantly associated with the increased risk of pre-eclampsia in recessive model (AA vs. AG + GG: OR = 1.522 [95% CI: 1.089–2.127]; $p = 0.014$), co-dominant model (AA vs. GG: OR = 1.605 [95% CI: 1.102–2.336]; $p = 0.014$), and allelic model (A vs. T: OR = 1.200 [95% CI: 1.021–1.402]; $p = 0.021$).

Conclusions. In summary, COMT Val158Met polymorphism is positively associated with the increased risk of pre-eclampsia among pregnant women, especially the homozygous carriers. It could be of value to investigate its association with pre-eclampsia in combination with additional risk factors. However, very large studies with different ethnic population are required to accurately demonstrate the role of this candidate gene in development of pre-eclampsia.

Key Words: Pre-eclampsia, Catechol-O-methyltransferase, Meta-analysis.

Introduction

Hypertensive disorders of pregnancy (HDP) are important complications of pregnancy, which are classified into different categories including excessive chronic hypertension, hypertension during pregnancy, chronic hypertension, regular increase in chronic hypertension, pregnancy hypertension, pre-eclampsia and eclampsia (1).

Pre-eclampsia is a pregnancy-specific disease that affects about 5–8 percent of pregnant women worldwide (2). The disease generally can be identified with high blood pressure and proteinuria after the twentieth week of pregnancy (3,4). Pre-eclampsia is mainly associated with congenital disorders such as liver, kidney and brain failure in the fetus, which are important factors of death in mother and fetus (3). This disease is a heterogenic multi-system disease (1,4) and like other complex disorders, genetic and environmental factors such as maternal characteristics including pregnancy age and weight before pregnancy are associated with the risk of this disease. Oxidative stress and the inflammatory response that occurs due to ischemic of placental blood flow may also be involved in the

Address reprint requests to: Ali Taravati, Department of Molecular and Cell Biology, Faculty of Basic Sciences, University of Mazandaran, Babolsar, 47416-95447, Iran; Phone and FAX: +98-1135302450; E-mail: a.taravati@umz.ac.ir.

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2017.03.006

pathogenesis of pre-eclampsia, but the main cause is still unknown (5). Studies have shown that underlying factors such as kidney disease, diabetes or chronic hypertension increases the risk of pre-eclampsia in pregnant women (3). However, genetic factors are responsible for more than 50% of the causes. Various studies have shown the role of several genes that may be involved in this disorder, but the results are contradictory and the candidate genes for this disease have not been diagnosed properly (1,4). It is believed that different genes including angiotensin (AGT), nitric oxide synthase (NOS), methylenetetrahydrofolate reductase (MTHFR) and catechol-O-methyltransferase (COMT) have been involved in the development of pre-eclampsia (2).

Angiotensin is an oligopeptide which is derived from the angiotensinogen and involved in secretion of vasopressin and catecholamine (6). This hormone increases blood pressure by vascular constriction. It also stimulates the secretion of aldosterone which is involved in the increasing of blood pressure (7). COMT is a key enzyme in degradation pathways of estrogens and catecholamines (2,4). This enzyme is composed of 271 amino acid encoded by a gene of the same name which is located on chromosome 22 within band 22q11.2. COMT is expressed in many tissues and participate in various physiological processes such as lipid metabolism, inactivation of catechol amines and cerebral cortex activity (5). This enzyme has an effective role in preventing cardiovascular disease (4). It is evidenced that the changes of single base in coding sequence of COMT may lead to an increase or decrease in the enzyme activity (5). So, it could be suggested that mutations in COMT gene would increase the risk of pre-eclampsia and cardiovascular disease (1). COMT catalyzes transfer methyl groups from S-adenosyl methionine to hydroxyl group at the core of catechol and thus inactivates catechol amines. So, it plays an important role in the regulation of dopaminergic system in many tissues including liver and kidney (8). 2-methoxyestradiol (2-ME) is an endogenous active metabolite of estradiol (4), which is produced by methylation of the catechol ring in beta estradiol by COMT. It has a low estrogenic activity due to very little affinity for estrogen receptors (9). Since steroid hormones have an important role in the maintenance and progress of pregnancy, their imbalance or inactivation may cause various diseases such as pre-eclampsia (10). 2-ME was proposed as a factor for regulation of hypoxia induced genes expression through inhibition of the HIF-1α gene expression in the placenta (11). In the normal condition the 2-ME concentration increases in line with pregnancy hormones, while reduction in 2-ME level was reported in women with pre-eclampsia (11,12). Low concentration of 2-ME lead to impaired inhibition of the HIF-1α expression, which consequently would accompanied with lowered placental oxygen level, disruption of normal angiogenesis and occurrence of pre-eclampsia.

COMT enzyme exists in two isoforms: a soluble form (S-COMT) and a membrane-bound (MB-COMT) (13,14). MB-COMT is longer form, which is produced by nerve cells in the brain but S-COMT is shorter form and expresses in liver, kidneys and blood, which is involved in controlling the levels of main hormones. Several polymorphisms may occur in coding and noncoding sequences of COMT; each of them has different effects on enzyme activity. For example, one SNP in the intron 1 of SB-COMT that affects gene expression was reported to be associated with increasing risk of schizophrenia (14). Other common functional polymorphisms at position 472 on exon 4 of this gene is substitution of A−G (G > A, rs4680) that results in a substitution of valine to methionine at amino acid position 158 (Val158Met) (15). Several studies have shown that methionine allele will reduce enzyme activity in comparison with valine allele (8,16). This substitution has shown that it is associated with 3−4 fold reduction in enzyme activity, which is leading to a decrease in natriuresis and increase in blood pressure due to adverse dopaminergic reactions in kidneys (8). It has also shown that the reduction

Table 1. Summary ORs and 95% confidence interval of the association between polymorphism in the COMT G472A gene and pre-eclampsia risk

	Studies	Odds ratio	95% confidence interval	*p*	Statistical model	I^2 (%)	P_{Het}
AA + AG vs. GG (dominant)	5	1.061	0.951−1.184	0.288	Fixed	41.47	0.128
		1.129	0.954−1.335	0.158	Random		
AA vs. AG + GG (recessive)	5	1.228	1.074−1.403	0.003	Fixed	66.28	0.011
		1.522	1.089−2.127	0.014	Random		
AA vs. GG	5	1.250	1.059−1.474	0.008	Fixed	67.86	0.008
		1.605	1.102−2.336	0.014	Random		
AG vs. GG	5	1.005	0.895−1.128	0.935	Fixed	2.14	0.402
		1.007	0.894−1.133	0.909	Random		
Over-dominant	5	0.932	0.843−1.030	0.170	Fixed	0.00	0.439
		0.932	0.843−1.030	0.170	Random		
A vs. G (allele)	5	1.099	1.020−1.184	0.013	Fixed	64.63	0.015
		1.200	1.028−1.402	0.021	Random		

P_{Het}, *p*-value for heterogeneity test.