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ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 708–711
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Catechol *O*-methyltransferase val158-met polymorphism is associated with abdominal obesity and blood pressure in men

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Received 5 July 2007; accepted 7 January 2008

Abstract

Catechol *O*-methyltransferase (COMT) degrades catecholamines and estrogens, both of which are of known importance for cardiovascular risk factors such as obesity and hypertension. The gene coding for COMT contains a val158-met polymorphism that exerts a considerable influence on enzymatic activity. We hypothesized that this polymorphism might influence risk factors for cardiovascular disease. Deoxyribonucleic acid samples and data regarding blood pressure and anthropometry were collected from 240 Swedish men, all 51 years old. Subjects homozygous for the low-activity allele (met) displayed higher blood pressure, heart rate, waist-to-hip ratio, and abdominal sagittal diameter as compared with heterozygous subjects, who in turn displayed higher blood pressure, heart rate, waist-to-hip ratio, and abdominal sagittal diameter than subjects homozygous for the high-activity allele (val). All measured variables were significantly correlated; however, the associations between COMT val158-met and cardiovascular variables, and the association between COMT val158-met and anthropometry, respectively, were partly independent of each other, as revealed by multiple linear regression.

1. Introduction

Cardiovascular disease is one of the leading causes of morbidity and mortality. A better understanding of its etiology could lead to improved prevention and treatment strategies. Some of the known cardiovascular risk factors, such as obesity and hypertension, are in part genetically determined; but the specific genes involved remain to be identified.

Catechol *O*-methyltransferase (COMT) is an omnipresent enzyme of importance for the degradation of both catecholamines and estrogens [1]. Because both catecholamines and sex steroids exert well-established influences on food intake [2] and metabolism [3], it is not farfetched to suggest that the activity of the COMT enzyme may influence body mass index (BMI) and/or fat distribution in man. In addition, given the well-known influence of catecholamines on the cardiovascular system [4,5], COMT activity being of importance for blood pressure regulation also is likely. In line with the latter notion, recent studies suggest that hypertensive rat strains display decreased COMT activities as compared with normotensive rats [6,7] and that knockout mice lacking the COMT gene are resistant to salt-induced hypertension [8]. Whereas studies on healthy individuals have not been able to show any significant effect on blood pressure of the COMT inhibitor entacapone, one study suggests that this compound may elicit a moderate, dose-dependent pressor response in patients with impaired baroreflex buffering [9].

The gene coding for human COMT contains a single nucleotide polymorphism in the fourth exon leading to a val to met amino acid change (val158-met). Whereas met/met carriers display a 3-to 4-fold reduction in catecholamine-degrading enzymatic activity as compared with val/val carriers, heterozygotes display intermediate enzymatic

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doi:10.1016/j.metabol.2008.01.012

activity [10]; moreover, the met allele seems to be less active than the val allele also with respect to estrogen degradation [11]. To explore to what extent the COMT val158-met polymorphism may influence cardiovascular risk factors, we investigated its possible association to BMI, sagittal diameter, waist-hip ratio (WHR), and blood pressure in 240 middle-aged Swedish men, all 51 years old, who were recruited by means of the population register and free from antihypertensive medication.

2. Materials and methods

2.1. Subjects

In 1992, all men born during the first 6 months in 1944 and living in Göteborg, Sweden (n = 1302), were identified using the National Population Registry [12]; 1040 men (80%) responded to a questionnaire sent out by mail. Based on self-measured WHR, 3 subgroups, each comprising 150 men, were selected: those with the lowest WHR (≤0.885), the highest WHR (≥1.01), and median WHR (0.94-0.96). These individuals were invited to a health examination in 1995. Two hundred seventy-five volunteered to participate both in health examinations and genetic studies, but 35 of these could not be genotyped because of insufficient blood samples. Twenty-six of the remaining 240 subjects were taking one or more antihypertensive drugs at the time of the study and were therefore excluded. Because the inclusion of subjects was based on self-rated rather than verified WHR, the laboratory-assessed WHR data in the studied population did not comprise 3 distinct groups, as was the case when the patients were included on the basis of self-measured values. All participants gave written informed consent. The study was approved by the Ethics Committee, Göteborg University, Sweden.

2.2. Clinical measurements

All examinations were performed in the morning after an overnight fast and carried out by the same research nurses and technicians.

Systolic and diastolic blood pressure (millimeters of mercury) was measured twice on the right arm with participants in a sitting position, with a 5-minute rest before and between readings. A random-zero mercury sphygmomanometer was used, and heart rate was recorded simultaneously. Mean values of the 2 recordings were used for statistical analysis.

Body weight was measured to the nearest 0.1 kg, height was measured to the nearest centimeter, and BMI was calculated based on these measures (kilograms per square meter). The waist circumference was measured halfway between the lowest rib and the iliac crest, and the hip circumference over the trochanters, allowing assessment of WHR. The abdominal sagittal diameter (millimeters) was determined as the distance between the examination table and the highest position of the abdomen.

2.2. Molecular genetics

Deoxyribonucleic acid was isolated from whole blood by Qiagen Genomic DNA Purification Kit (Qiagen, Chatsworth, CA). Polymerase chain reactions were carried out using HotstarTaq polymerase (Qiagen) in a total volume of 20 μL containing 1.5 mmol/L MgCl2, 0.15 μmol/L primers (forward: 5′-TCA CCATCGAGATCAACCCC-3′, reverse: 5′-ACAACGGGTCAGGCATGC A-3′), and approximately 50 ng genomic DNA. After an initial 15-minute denaturation step at 95°C, 45 cycles were performed including 30 seconds at 94°C, 30 seconds at 62°C, and 30 seconds at 72°C. The polymerase chain reaction products were genotyped with the Pyrosequencer PSQ 96 and the PSQ 96 SNP Reagent Kit (Pyrosequencing, Uppsala, Sweden) using the sequence primer 5′-TGG TGG ATT TCG CTG-3′ [13].

2.3. Statistical analysis

As the COMT val158-met polymorphism is known to result in 3 phenotypes with high, intermediate, and low activity, linear regression was used to analyze the relationship between the COMT val158-met polymorphism and the various phenotypes. The genotypes were coded 0, 1, or 2 according to the count of the val allele. Correlation analyses were made for the different phenotypes.

3. Results

Genotype distribution is presented in Table 1. The allele frequencies for the entire population were val = 45.6% and met = 54.4%, which are similar to the frequencies previously reported in Swedish studies [11]. The COMT val158-met polymorphism was significantly associated with WHR and abdominal sagittal diameter—but not with BMI—those being homozygotes for the low-activity allele (met) displaying the highest WHR and sagittal diameter, and those being homozygotes for the high-activity allele (val) displaying the

Table 1
Phenotypic characteristics of the COMT val158-met polymorphism in men (individuals taking antihypertensive drugs excluded)

Variables	val/val (n = 42)	val/met (n = 117)	met/met (n = 55)	*P* values	r^2 values
Systolic blood pressure	121.7 ± 12.0	127.9 ± 16.1	131.7 ± 19.2	.003	0.04
Diastolic blood pressure	80.0 ± 9.6	83.0 ± 10.1	84.7 ± 10.4	.03	0.02
Heart rate (beats/min)	65.7 ± 9.8	69.3 ± 10.6	70.7 ± 10.3	.02	0.02
BMI (kg/m2)	25.6 ± 3.5	25.9 ± 3.8	26.3 ± 4.3	.3	0.004
WHR	0.91 ± 0.07	0.93 ± 0.07	0.96 ± 0.07	.002	0.04
Abdominal sagittal diameter (mm)	214 ± 36	225 ± 34	229 ± 38	.05	0.02

Mean values ± standard deviations. *P* values are based on linear regression.

lowest (Table 1). A similar difference between the 3 genotypes was found also with respect to cardiovascular parameters, the met allele being associated with higher systolic blood pressure, diastolic blood pressure, and heart rate (Table 1).

All variables displayed in Table 1 correlated with each other (data not shown). The correlation between the 2 parameters most strongly related to the COMT val158-met polymorphism, that is, systolic blood pressure and WHR, was $r = 0.26$ ($P < .0001$). When systolic blood pressure was regressed on both WHR and the COMT val158-met polymorphism, the slope for the allele count remained significant ($P = .023$) and was estimated to be 3.8 mm Hg per met allele. When, on the other hand, WHR was regressed on both systolic blood pressure and the COMT val158-met polymorphism, the allele count again remained a significant predictor ($P = .017$). This outcome indicates that the COMT val158-met is independently associated with both blood pressure and anthropometry, influencing these 2 variables through partly independent mechanisms.

4. Discussion

In the present study, we found associations between the COMT val158-met polymorphism to be associated with systolic and diastolic blood pressure, heart rate, and body fat distribution in a sample of middle-aged Swedish men. These findings are intriguing because COMT plays an important role in the degradation of catecholamines and estrogens, which both are involved in cardiovascular control and fat distribution [2,3,5,14,15].

The strongest associations were found between the COMT val158-met polymorphism and systolic blood pressure, and between COMT val158-met and WHR. The difference in mean in systolic blood pressure between the met/met and the val/val group was of a clinically relevant magnitude (10 mm Hg), as was the difference in WHR (0.04). In the cases where influences of specific polymorphisms on complex, multifactorial traits have been established, the studied polymorphism usually has not contributed more than 5% to 10% of the observed variance.

Abdominal obesity is believed to be a greater cardiovascular risk than obesity per se. The current finding that there was a significant association between the studied polymorphism and WHR, but not BMI, supports the notion that weight and fat distribution are regulated by partly different genes.

One previous study assessing the possible association between the COMT val158-met polymorphism and BMI did not find any such relationship and is hence in line with our results [16]; in contrast, Tworoger and coworkers [17] reported the exercise-induced weight loss in women to be slightly smaller in met carriers. To what extent the COMT val158-met polymorphism is associated with WHR has been assessed in a previous study by Hong and coworkers [18] in which WHR was one of a number of risk factors for breast cancer assessed in 350 women. The results obtained in premenopausal women regarding the relationship between the COMT val158-met polymorphism and WHR in this study are in consonance with the results we obtained in middle-aged men, the met allele being associated with higher WHR in a dose-dependent manner. It should however be noted that Hong and coworkers did not find the same relationship in postmenopausal women. Moreover, they did observe an association between the COMT val158-met polymorphism and BMI in the premenopausal group; this association however was weaker than that observed for WHR and disappeared after adjustment for levels of growth hormone and insulinlike growth factor–1. In a study by Happonen and coworkers [20], no marked effects of the COMT val158-met polymorphism on WHR were found.

Our results showing association between the met allele of the COMT gene and high blood pressure are coherent with investigations in rodents where hypertensive animals have been reported to display reduced COMT activity in kidney [7] as well as in the brain [6]. In contrast to our results and to these data from animal experiments, Hagen and coworkers [19] recently reported an association between high COMT activity and hypertension, the val/val genotype being overrepresented in individuals with systolic hypertension (≥140 mm Hg) in the age groups 40 to 49 and 80+ years. In line with our finding, but in contrast to that of Hagen and coworkers, Happonen and coworkers [20] have reported male met/met carriers to display marginally higher systolic blood pressure. Noted should also be a study by Kamide and coworkers [21] reporting no significant association between the COMT val158-met polymorphism in a Japanese population; they however did report an association between certain haplotypes of this gene and blood pressure.

The reason for our failure to replicate the finding of Hagen and coworkers, but instead finding a highly significant association in the opposite direction, is not obvious. It should, however, be taken into consideration that their cohort, being considerably larger than ours, comprised both sexes and subjects of different ages; moreover, the association reported in that trial was weak and apparent in certain age segments only. A polymorphism being repeatedly found to be associated to a certain phenotype, but studies from different laboratories yielding associations in different directions, is not uncommon and may be the consequence of other gene variants influencing how the polymorphism in question influences the studied trait.

Our finding that 2 risk factors for cardiovascular disorders are independently associated with the met allele of the COMT val158-met polymorphism gains indirect support from 2 recent Finnish studies of large samples showing met carriers to display an increased risk for acute coronary events [20,22]; moreover, in the abovementioned study by Hagen and coworkers [19], there was a tendency for val/val carriers to display lower prevalence of heart diseases (despite the fact

that this genotype in that study was associated with hypertension). On the other hand, Eriksson and coworkers [11] found the val allele to be protective against myocardial infarction; this observation however was made in a cohort comprising hypertensive subjects only and is hence not directly comparable with findings in other cohorts.

Whereas the main weakness of our study is the small size of the studied population, the fact that the cohort was very homogenous with respect to sex, age, and ethnicity may be regarded as a strength, enhancing the likelihood to detect an association between genotype and phenotype. Whereas the association found between the COMT val158-met polymorphism and WHR was in line with a previous study in women, the association between this polymorphism and blood pressure was in contrast to a previous study. The high level of statistical significance for the associations found in this homogenous cohort and the fact that the COMT val158-met polymorphism was independently associated with both WHR and blood pressure make further studies on the possible relationship between this polymorphism and cardiovascular risk factors warranted.

Acknowledgment

This project is supported by the Lundberg Foundation, Swedish Lundbeck foundation, Knut and Alice Wallenberg Foundation, the Swedish Brain Power Consortium, and the Swedish Medical Research Council (8668).

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