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ORIGINAL ARTICLE

Relationship between oxytocin receptor gene polymorphism and hypertension in Turkish population

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KEYWORDS
Oxytocin;
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Abstract
Introduction and objectives: Known to play a key role in uterine contraction and milk ejection, the neuropeptide, oxytocin, has cardiovascular effects. To date, the known cardiovascular effects of oxytocin are blood pressure lowering (caused by natriuresis and atrial natriuretic peptide release), negative inotropic and chronotropic effect caused by parasympathetic neuromodulation, anti-stress effect and vasodilation mediated by activation of the nitric oxide pathway. The clinical significance of the rs2268498 polymorphism in oxytocin receptors in these effects is controversial. Based on the known genetic inheritance of hypertension, our research aimed to determine whether the presence of the rs2268498 oxytocin receptor (OXTR) allele C affects hypertension in our region.
Methods: This article is a case-control study conducted in the Turkish population. About 140 normotensive and 140 isolated hypertensive volunteers included in the research and genotyped with real-time PCR hybridization method via melt curve analysis.
Results: Oxytocin receptor rs2268498 polymorphism was assessed in terms of the risk of hypertension and hypertensive individuals were compared to the control group. OXTR rs2268498 polymorphism was not found to be a significant risk factor for dominant, recessive and additive modeled hypertension ($OR_{dominant}$: 0.966, 95% CI: 0.57-1.61, p: 0.9; $OR_{recessive}$: 1, 95% CI: 0.58-1.71, p: 1.0 and $OR_{overall}$: 0.98, chi^2=0.01).
Conclusion: We concluded that rs2268498 single nucleotide polymorphism is not a risk factor for hypertension in our region.

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PALAVRAS CHAVE
Ocitocina;
Hipertensão essencial;
Doenças vasculares

Relação entre o polimorfismo do gene recetor da ocitocina e a hipertensão na população turca

Resumo
Introdução e objetivos: Conhecido por desempenhar um papel fundamental na contração uterina e na ejeção de leite, o neuropéptido ocitocina apresenta efeitos cardiovasculares. Até ao momento, os efeitos cardiovasculares conhecidos da ocitocina são a diminuição da pressão arterial (causada pela natriurese e libertação do péptido natriurético auricular), o efeito inotrópico e cronotrópico negativo por neuromodulação parassimpática, o efeito anti-stress e a vasodilatação mediada pela ativação da via do óxido nítrico. O significado clínico do polimorfismo rs2268498 nos recetores de ocitocina nestes efeitos é controverso. Com base na conhecida herança genética da hipertensão arterial, a nossa pesquisa visou determinar se a presença do alelo C do recetor de ocitocina (OXTR) rs2268498 afeta a hipertensão arterial na nossa região.
Métodos: Estudo caso-controlo realizado na população turca. Foram incluídos na pesquisa 140 voluntários normotensos e 140 hipertensos isolados e genotipados com Método de Hibridização PCR em Tempo Real via Análise de Curva de Melt.
Resultados: O polimorfismo OXTR rs2268498 foi avaliado em termos de risco de hipertensão e os hipertensos foram comparados com o grupo controlo. O polimorfismo OXTR rs2268498 não demonstrou ser um fator de risco significativo para hipertensão dominante, recessiva e aditiva modelada (OR dominante: 0,966, % 95 CI: 057-1,61, p: 0,9; OR recessivo: 1, % 95 CI: 0,58-1, 71, p: 1,0 e OR total: 0,98, chi^2=0.01).
Conclusão: O polimorfismo de nucleotido único rs2268498 não é um fator de risco para hipertensão na nossa região.

Introduction

Oxytocin is a neuropeptide synthesized in the hypothalamus, especially the paraventricular and supraoptic nucleus.[1] It was discovered by the Italian scientist Nicolas Ferraye in 1835 and its molecular formula is $C_{43}H_{66}N_{12}O_{12}S_2$.[2] The neuropeptide is released from the posterior pituitary into the systemic circulation and acts as a hormone with physiological effects on the body.[1] The target regions of oxytocin, a cyclic nano peptide, include the region that regulates the autonomic nervous system of the hypothalamus, brainstem, heart, uterus, and spinal cord that regulates the parasympathetic nerve.[3] Although circulating oxytocin is known to initially stimulate uterine contractions and milk ejection in lactation to initiate delivery, it was later recognized that there were similar numbers of oxytocinergic neurons in the female and male hypothalamus and that the same stimuli induced oxytocin release in both genders.[4] Oxytocin-containing axon terminations were then detected in nuclei in some parts of the central nervous system. These axon terminations were found to play a role in cardiovascular control. Further evidence that oxytocin plays a role in cardiovascular regulation was revealed with the discovery that it is produced and released from certain regions in the brain and (caused by parasympathetic neuromodulation), all four chambers of the heart.[5]

The known cardiovascular effects of oxytocin are decreased blood pressure (caused by natriuresis and atrial natriuretic peptide release), negative inotropic and chronotropic effects (caused by parasympathetic neuromodulation), anti-stress effect, and endothelial cell growth oxytocin-induced vasodilation that occurs with activation of a nitric oxide pathway.[6,7] As a cardiovascular risk factor, hypertension is a metabolic disorder that is characterized by arterial blood pressure (BP) values measured at certain frequencies above 140/90 mm Hg, also known to lead to co-morbid cardiovascular diseases (heart failure, coronary heart disease, stroke, aortic dissection, etc.).[8,9] It usually occurs in the 50-60 age range of life and is associated with increased salt consumption, obesity, and genetic predisposition.[10] It has been stated that the effect of genetics on blood pressure variations is 20-40%.[11] 90% of hypertension cases are essential hypertension.[9] It is a type of hypertension that cannot be attributed to any secondary cause such as essential hypertension, renovascular diseases, Cushing's syndrome, and is also known as idiopathic hypertension.[12] In some cases (10-20%), secondary hypertension resulting from pathological conditions (Cushing's syndrome, renal artery stenosis, renal parenchymal disease, etc.) is observed.[13]

Blood volume and pressure regulation depend on oxytocin secretion. Maisel et al. showed that decreased oxytocin expression in a spontaneously hypertensive rat hypothalamus correlated with the development of hypertension.[14] Bernatova et al. (2009) demonstrated that oxytocin knockout mice had higher blood pressure in stress conditions.[15] Szeto et al. (2008, 2013) demonstrated the protective effects of oxytocin on atherosclerotic lesion development in cell culture and animals.[16,17] Wigger et al. (2020) revealed that the oxytocin receptor (OXTR) gene expression in smooth

muscle cells of arterioles affects blood pressure regulation through changes in vessel diameter.[18] A study examining the cardiovascular consequences of resistance exercise found that physical exercise decreased blood pressure, vascular resistance, heart rate, and increased release of endothelium-derived relaxing factors. It has been stated that this exercise method increases the amount of oxytocin receptor mRNA in the medulla and increases the release of oxytocin from the paraventricular nucleus. This exercise response in the cardiovascular system has been associated with oxytocin-dependent baroreflex control and reduction of sympathetic tone.[19]

The OXTR gene is a 17 kb span, a single-copy gene with three introns and four exons located at 3p25-3p26.2 gene loci.[20] Stress, related diseases were found to be associated with the OXTR gene.[21] Studies conducted to date show that polymorphisms in the oxytocin and OXTR are associated with social abilities, impairments, and autistic behaviors.[22,23] It has been observed that the oxytocin/oxytocin receptor system is impaired in most patients with autism spectrum conditions. However, there has been no assessment of the strength of OXTR rs2268498 polymorphism associated with the development of hypertension.

We therefore decided to conduct a case-control study to investigate the risk of hypertension and rs2268498 C/T single nucleotide polymorphism found in the promoter region of the OXTR gene. Previous studies mentioned that OXTR rs2268498 polymorphism had been associated with social cognitive and affiliative phenotypes and atypical social behaviors such as autism spectrum disorders.[24,25] To the best of our knowledge, no studies have been conducted on hypertension, so our study is the first report in the literature.

Material and methods

Study population

This article is a case-control study conducted in the Turkish population. Inclusion criteria for the patient group in this study (n=140; the average age of 64.01±9.48 years) were to have been newly diagnosed by a health professional or under long-term primer essential hypertension treatment. According to the World Health Organization/International Hypertensive Union Hypertension Congress, a diagnosis of hypertension is made according to average systolic blood pressure and diastolic blood pressure >140 mm Hg and >90 mm Hg, respectively. The volunteers in the study group were primary hypertension patients (not attributed to a secondary cause), did not have obesity and renal impairment, whose daily salt consumption was at the desired value, and whose hemodynamic and physiologic components did not have any deviations that might cause hypertension. Inclusion criteria for the control group were (n=140; 56.41±12.85) > 18 years of age and no history of hypertension or cardiovascular disease. Pregnancy and breastfeeding were exclusion criteria for both the patient and control study groups. All participants were informed about the study and written informed consent was collected. Simple random sampling was used for randomization.

Our study was approved by Canakkale Onsekiz Mart University Clinical Researches Ethical Committee under number 2018-17, dated 10.10.2018. The study was conducted according to the principles of the Declaration of Helsinki.

Protocol

Genomic deoxyribonucleic acid (DNA) from each subject was purified from the venous blood. Two ml of blood from each participant were drawn into EDTA anticoagulated tubes, stored at -20°C until the day of assay. According to the manufacturer's instructions, a commercial kit was used to perform the genomic DNA purification (GF-BD-100 Blood DNA Extraction Kit, Diagen). Before the PCR protocol, samples were removed on an ice battery. When melting was complete, DNA samples were mixed via short-term vortexing. As a result of DNA quantification, each sample was prediluted to be 20 ng/μl so that all samples were at the same concentration. Then genotype analyses were performed with real-time-PCR using a hybridization probe method via melt curve analysis (Roche LightCycler 2.0; Roche Diagnostics, Penzberg, Germany).

Primer design

Primer design was performed by using the Primer3 Design program. While amplifying the target fragments, the following primers and probes were used:

Forward primer: 5′-ACCGGTCAGGGGCTCATA-3′;

Reverse primer: 5′-TGTGCAATCTGAGGGTTCAA-3′;

Anchor hybridization probe: 5′-LCRed640-CTGGATGAAGGCAGATTTTTCCCTATGAphosphate-3′;

Sensor hybridization probe [C]: 5′-AAAACACC_GCCTCACCCCACG-FAM3′.

An analysis of selected rs2268498 single nucleotide polymorphisms of the OXTR gene was carried out under the protocol at the device (Roche Lightcycler 480 II (Switzerland)).

Briefly, by adding in a total volume of 5 μl, 10 ng DNA, 0.5 μM sense and antisense primer with 0.2 μM anchor and sensor probe, 0.5 μl 10× reagent mix, 0.2 mM dNTP, 4.0 μM $MgCl_2$, 0.5 U of DNA polymerase were used, and PCR reaction was performed. The cycle conditions were as follows: initial denaturation for 10 min at 95°C and followed by 40 cycles of 15 s at 95°C, 55°C for 15 s, 72°C for 15 s with a final 2-min extension at 72°C. As a final process, melt curve analyses were performed by denaturation and annealing at 94°C for 60 s; at 40°C for 60 s. Melting was performed by heating from 40 to 80°C at a rate of 0.1°C/s. After the samples were programmed and analyzed with the appropriate parameters, the readings were determined. The melting temperature was 46°C for the T allele and 54°C for the C allele in rs2268498. Alleles and genotypes were assigned as if the melting curve temperature is 46±1°C for TT allele (wild allele), the mutant allele (minor allele) is 54±1°C for CC allele, and the melting curve temperature is 54±1°C and 46±1°C for the heterozygous allele CT allele.

Table 1 Distribution of oxytocin receptor rs2268498 genotypes and alleles in the hypertensive and control group.

	Hypertension n=140 (expected %)	Control n=140 (expected %)	p value	OR [95% CI]
OXTR Genotypes				
Mutated C/C	35 (31.59%)	35 (32.06%)	p=0.941[a] χ^2: 0.01	Homozygotous OR: 1.024 [0.542-1.935][a]
Mutated C/T	63 (69.83%)	64 (69.87%)	p=0.957[a] χ^2: 1.31	Heterozygotous OR: 0.984 [0.549-1.764][a]
Wild-type T/T	42 (38.59%) Reference group	41 (38.06%) Reference group	p=1.00[b]	Allele positivity OR: 1[0.582-1.718][b]
OXTR allele	*Hypertension group control group* Frequency of T: 0.525±0.031; Frequency of T: 0.521±0.031; p=0.247[d]; p=0.320[d]			
C allele (minor allele)	133	134	p: 0.933[c] χ^2: 0.01	OR: 1.014 [0.728-1.413][c]
T allele (wild type)	147 Reference group	146 Reference group		

CI: confidence interval; OR: odds ratio.
[a] p values and ORs for frequency differences in C/C or C/T versus wild-type T/T genotypes between case and control subjects.
[b] p values and ORs for frequency differences in G/T andC/C versus wild-type T/T genotypes between case and control subjects.
[c] p values and ORs for frequency differences in allele G versus wild-type T between case and control subjects.
[d] p values to determine genotype frequencies in hypertension/control group if fits Hardy-Weinberg equilibrium.

Statistical analysis

The statistical analysis was performed with Statistical Package for Social Sciences (SPSS) for Windows 19.0 (SPSS for Windows, SPSS, Chicago). Numeric data are expressed as mean (standard deviation). Allele frequencies were determined by the allele counting method then utilized to determine homozygous wild-type, heterozygous and homozygous mutant genotype frequencies of the OXTR gene. The differences between observed genotype frequencies and the expected ones were checked using the Chi-square goodness of fit (Hardy-Weinberg Equilibrium). The odds ratio (OR) association of the OXTR genotypes with hypertension was investigated (95% confidence intervals (CI)).Student-t-test was used for the differences between study groups, and the Chi-square test was used for quantitative data. Pearson correlation and Spearman's rank correlation coefficient were used to evaluate the correlation of variables. In case of $p<0.05$, the results were accepted as statistically significant.

Results

Allele and genotype frequencies of rs2268498 in 140 hypertensive patients and 140 healthy controls were determined in the Turkish population. Genetic expression analysis studies performed in human hippocampal tissues showed that OXTR mRNA transcription is two-fold different depending on the presence and absence of the C allele.[26] The risk allele (minor allele) for the OXTR gene rs2268498 region was accepted as ''C.'' The frequency of the C minor allele of rs2268498 was not found to be different between the hypertensive and control group, 0.475 and 0.479, respectively. Both cohorts were constant within the Hardy-Weinberg equilibrium. When evaluated in terms of difference in allele frequency, the relationship between OXTR rs2268498 polymorphism and hypertension risk was found not to be statistically significant (OR=0.986, 95% CI: 0.708-1.73) (Table 1).

The oxytocin receptor rs2268498 genotype distribution of the patient and control groups was examined, then the genotype frequency was compared. The genotype distribution of the control group was as follows: 41 volunteers in the TT allele genotype; 64 in the CT genotype; and 35 in the CC genotype. Thus, of the patients with hypertension, 42 out of 140 had the TT genotype, 63 had CT, and 35 had the CC genotype of the OXTR single nucleotide polymorphism (Table 1).

We have analyzed the genotype frequencies but there was no statistical difference in geneotype among the cohorts. There was no increased risk for hypertension in the dominant model (OR: 0.966, 95% CI (0.579-1.614)). The heterozygous CT genotype was the most frequent in both cohorts (63 cases in hypertensive patients and 64 in the control group). We established that the OR for hypertension was not different in heterozygotes than in wild-type genotype (OR: 0.961, 95% CI (0.553-1.671)). Also, when evaluated in terms of two minor alleles; there was no statistically significant relationship between OXTR rs2268498 polymorphism and hypertension risk (OR: 0.976, 95% CI (0.517-1.844). Based on our data, patients with the CC or CT genotype did not have an increased risk of hypertension (Table 1).

As a result, when OXTR rs2268498 polymorphism is evaluated in terms of hypertension risk, hypertensive individuals are appraised according to the control group. OXTR rs2268498 polymorphism is not a significant risk factor for

dominant, recessive and additive modeled hypertension respectively: ($OR_{dominant}$: 0.966, 95% CI: [0.57-1.61], p: 0.89; $OR_{recessive}$: 1, 95% CI: [0.58-1.71], p: 1.0 and $OR_{overall}$: 0.987, chi^2: 0.01, p: 0.93).

Discussion

Our study considered whether rs2268498 C/T single nucleotide polymorphism found in the promoter region of the OXTR gene affects the development of hypertension in individuals. In previous population studies, the frequency of the C allele was 0.25 in the Vietnamese population, 0.34 in the American population, 0.41 in the Ashkenazi Jews, 0.42 in the Estonian population, 0.43 in the Northern Swedish and 0.45 in the European population. Considering the minor allele frequency values, in light of the results observed in our study, the Turkish population is similar to the nearest European population for the patient and healthy control group.[24]

Jacondino et al. investigated another polymorphism in OXTR with the cardiovascular risk factors in the Brazilian population. They hypothesized that oxytocin positively affects hemodynamic mechanisms by regulating blood pressure and releasing atrial natriuretic peptide. Jacondino et al. concluded that the incidence of hypertension in individuals with rs2254298 polymorphism was not statistically significant (p=0.569).[26] Similar to the previous study investigating different single nucleotide polymorphism on the same gene, we could not find significant differences in allele and genotype frequencies.

A study investigating the effects of rs2254298 single nucleotide polymorphism on OXTR expression and oxytocin levels in late term and term pregnant women observed that this polymorphism had no effect on the time of delivery. It was also unable to reach statistical significance in terms of its effect on OXTR expression and oxytocin levels.[27]

Regarding rs2268498 polymorphism, the OXTR expression levels of individuals in hippocampal tissue with the C allele, which is the risk allele, were found to be almost two times higher than the TT genotype carriers.[25] The lack of a study evaluating the effect of rs2268498 single nucleotide polymorphism on oxytocin level does not make it possible to compare the subject together with oxytocin levels. However, G protein coupled receptors – such as OXTR – compensate for prolonged exposure to the agonist by reducing or downregulating the number of receptors. The low amount of agonist belonging to the receptor causes receptor up-regulation, resulting in an increase in the number of receptors.[28] From this information, it is possible to evaluate the increase in OXTR expression levels as a physiological adaptation response to benefit more from the decreased oxytocin levels. In the literature, the protective effects of oxytocin on cardiovascular diseases and that reduced oxytocin level may expose the person to cardiovascular risk, support our hypothesis.

The importance of our study is because it is the first study to investigate OXTR rs2268498 C/T polymorphism with hypertension in the literature. For that reason, we would like to highlight that this novel analysis considers that OXTR rs2268498 is not a risk factor for hypertension in dominant, co-dominant, recessive models.

Study limitations

Studying reference sequences in other populations will more transparently demonstrate the OXTR rs2268498 C/T polymorphism effect on the risk of hypertension. However, in further studies, the study of the relationship of the complete sequence of the gene region with the risk of hypertension will be more precise to reveal the relationship between OXTR gene and hypertension more clearly.

Conclusions

When our risk allele is evaluated as the minor allele C, the results were not statistically significant between our patient and control group in terms of frequency values. In this respect, our study sheds light on the fact that having novel rs2268498 polymorphism does not affect hypertension in the Turkish population.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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