Neuroscience Letters 654 (2017) 28–32

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Are dopaminergic genotypes risk factors for eating behavior and obesity in adults?

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HIGHLIGHTS

- Obesity is becoming a serious health problem worldwide among individuals of all ages.
- This study reported significant cues for the relationship between obesity and gene polymorphisms of dopamine metabolizing enzymes.
- Our previous data suggested that DAT1 SNP (rs27072) might be a risk factor for the development of adult obesity.
- 'Eating for reward' might be related with obesity to compensate for modified dopamine neurotransmission.
- COMT Val/Met (rs4680) genotype was found to be protective for adult obesity.

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form 8 June 2017
Accepted 14 June 2017
Available online 16 June 2017

Keywords:
Obesity
Dopamine
MAOA
COMT
Reward
Eating behavior

ABSTRACT

Dopamine (DA) is the main modulator of the brain reward system and significantly regulates food intake. The idea that obesity is a neurobiological disease rather than a metabolic disorder, is the basis of the study. Changes in dopamine neurotransmission affect the brain reward system in a direct way. Furthermore, changes in the reward system influence the eating behavior in human. The enzymes monoamine oxidase A (MAOA) and catechol-O-methyltransferase (COMT) terminate the DA function by metabolizing it. In our study, the control group which included 214 individuals and 234 subjects with obesity were investigated for *MAOA-u* VNTR and *COMT* (rs4680) polymorphisms. In our study, statistical analysis has showed that in control group Val/Met COMT genotype was significantly higher compared with the patient group ($p = 0.04$). When the groups were compared in terms of eating behavior, the number of the subjects who ate for reward was significantly higher in patient group ($p = 0.03$). Our findings demonstrated that eating behavior might have an effect on obesity and dopaminergic polymorphisms could be risk factors for the development of obesity in Turkish population.

1. Introduction

Obesity is a health problem which is increasingly becoming prevalent in the worldwide and risky for several diseases such as cardiovascular diseases and cancer [1]. Obesity might be defined as neurobiological disease rather than metabolic disorder. For several years, individuals with obesity were considered that they had metabolic disturbances such as low metabolic rate. Additionally, scientists supposed that obesity could be an eating disorder such as binge eating, bulimia nervosa, night eating disorder [2–4].

The neurotransmitter dopamine is the main component of the neurobiological aspect of obesity. Palatable foods activate the reward system in the brain and contribute to the release of DA in striatum and nucleus accumbens [5]. Food intake activates the reward circuits and the expenditure of highly palatable and high calorie foods elevates the amount of dopamine in the brain and activates reward-related pathways, resulting in the reinforcing effects of euphoria or pleasure [6,7]. Food-related stimuli activates the brain centers which take roles for the synthesis, release or projections of dopamine [8]. Thus, identifying the genetic components of obesity and eating behavior can assist the development of prevention and treatment strategies by characterizing high-risk populations.

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http://dx.doi.org/10.1016/j.neulet.2017.06.023
0304-3940/

Table 1
Demographic characteristics of the study population.

Characteristic	Controls (n = 214)	Patients (n = 234)	*p*-value	OR
Sex				
Female	n = 166 (54.2%)	n = 140 (45.8%)	<0.001	
Male	n = 48 (33.8%)	n = 94 (66.2%)	<0.001	
Age (years)	27,8 ± 5,9	31,4 ± 7,9	<0.001	
BMI (kg/m^2)	21,7 ± 1,9	34,4 ± 8,7	<0.001	
Family history				
Yes	n = 82 (36.6%)	n = 142 (63.4%)	NS	0.815
No	n = 132 (59%)	n = 92 (41%)		
Eating behavior				
Need	n = 56 (57.1%)	n = 42 (42.9%)	0.03	0.617
Reward	n = 158 (45.1%)	n = 192(54.9%)		
Regular exercise				
Yes	n = 11(78.5%)	n = 3(21.4%)	0.02	0.745
No	n = 203(46.7%)	n = 231(53.3%)		

COMT is a degrading enzyme and metabolizes DA to inactive compounds. The gene that encodes COMT has a polymorphism in codon 158 that substitutes a methionine for a valine amino acid (Val158Met), generating a less active enzyme and increased DA concentrations [9]. The Val allele has four times more COMT enzymatic activity than Met allele [10]. Monoamine oxidase A is also a DA degrading enzyme and localized in the outer mitochondrial membrane. [11]. The promoter region of this gene is localized on the short arm of X chromosome and includes 30 base pair variable number tandem repeats (VNTR) sequence with 2, 3, 3.5, 4, or 5 repeats [12]. While, 3.5 or 4 repeats allele has high MAO-A activity, 2, 3, or 5 repeats allele has low enzymatic activity [13].

In the present study, we aimed to determine the relationship between the gene variants of the metabolism of DA and obesity and eating behavior. The metabolizing enzymes terminate the action and function of DA. Therefore, we were interested in the enzymes MAO-A and COMT to be able to figure out the mechanism of obesity via DA neurotransmission. We are not aware of any eating disorders and obesity studies using the terms 'eating for reward' and 'eating for need'. On the other hand, there are reports of the associations between *MAO-A* and *COMT* polymorphisms and obesity and eating behavior [14,15]. There have been no studies about the relationship between *MAO-A*, *COMT* polymorphisms and obesity and eating behavior in Turkish population so far. We expect that our findings might be helpful for the determination of the role of DA in the pathogenesis of obesity and eating behavior and then these results might alter the treatment of obesity and its complications and eating behavior according to the DA neurotransmission.

2. Subjects and methods

2.1. Subjects

In this study, we have investigated the polymorphisms of MAO-A and COMT genes in 2 groups. Group 1 (n = 234) whose mean age was 31,4 ± 7,8 years contained overweight and individuals with obesity and the mean BMI was 33,8 ± 8,7 kg/m^2 (see Table 1). The control group selected from healthy individuals (n = 214) who were compatible with age and sex and BMI between 18.50 and 24.99. The mean age of the healthy group was 27,6 ± 5,8 years and the mean BMI was 21,7 ± 1,9 kg/m^2 (see Table 1). Inclusion criteria were: 1. giving informed consent, 2. age between 20 and 48 years, 3. 25 ≤ BMI <30 for overweight and ≥30 for obese group; BMI: 18.50-24.99 for control group. Exclusion criteria were: 1. previous use substance of abuse, 2. having a neurological or psychiatric disorder, 3. being pregnant or nursing, 4. being chronic alcoholic, 5. smoking, 6. using antihypertensive beta-blocker, 7. being menopausal, 8. having thyroid or diabetes problem 9. oral contraceptive usage. Permission for research was granted by the Bioethics Committee of Yeditepe University, Istanbul, Turkey (Decree no: 411, date of approval: 22/04/2014). Both men and women of Turkish origin, all volunteers, were collected at the Department of Endocrinology and Metabolism Disorders at Fatih Sultan Mehmet Education and Research Hospital in Istanbul, Turkey. All volunteers were measured and weighed with standard medical device. Informed written consent was obtained from all subjects according to the Declaration of Helsinki guidelines. We had face-to-face interviews with all of the participants during the period of August, 2014 and February, 2015. The participants reported motivations for food using a modified version of Testing of the Eating Motivation Survey (TEMS) [16].

2.2. Genotyping

DNA extraction was performed from peripheral blood samples which were recruited in tubes including ethylenediaminetetraacetic acid (EDTA). For DNA extraction, the DTAB-CTAB (Sigma-Aldrich, Taufkirchen, Germany) DNA extraction method was used. Purity was compared based on A260/A280 absorbance ratios in the range of 1.7–1.9. The 30 bp VNTR in the promoter region of *MAO-A* and Val158Met SNP of *COMT* were genotyped using Touch-down Polymerase Chain Reaction (PCR) with proper primers. The sequence of the forward primer of *MAOA-u* VNTR is 5′-CCCAGGCTGCTCCAGAAAC-3′ and the reverse primer is 5′-GGACCTGGGCAGTTGTGC-3′. The sequence of the forward primer of Val158Met *COMT* is 5′-TCGTGGACGCCGTGATTCAGG-3′ and the reverse primer is 5′-AGGTCGACAACGGGTCAGGC-3′. The PCR products of *MAOA-u*VNTR were determined by agarose gel electrophoresis which was stained with ethidium bromide and then visualized under ultraviolet light.

The map of the restriction enzyme was found by the use of NEBcutter V2.0 program and the proper enzyme was selected according to the recognition sequence. The PCR products of rs4680 were cleaved by using NlaIII restriction enzyme. The restriction products were determined by agarose gel electrophoresis which was stained with ethidium bromide and then, visualized under ultraviolet light. The restriction fragments for Val/Val genotype were 136 and 81 bp; for Val/Met genotype were 136, 96, 81, and 41 bp; for Met/Met genotype were 96, 81, and 41 bp.

2.3. Statistical analysis

The statistical assessment of our study was carried out by the use of SPSS (Statistical Package for the Social Sciences) version 24.0 (Chicago, IL, USA). The differences of genotype between control and patient groups were analyzed by Chi-square, Fisher's Exact test.