The influence of the fatty acid amide hydrolase 385C>A single nucleotide polymorphisms on obesity susceptibility

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Abstract
The chronic over-activation of the endogenously produced cannabinoids in obesity has been demonstrated in several studies. A common 385C>A single nucleotide polymorphism of the fatty acid amide hydrolase, one of the most important inactivating enzymes of endogenous cannabinoids, has been shown to be associated with obese phenotype. This study was designed to investigate the FAAH gene polymorphisms and to compare the obesity indices between different genotypes in Iranian overweight/obese women. A total of 180 healthy overweight/obese subjects (BMI = 25 to 40 kg/m²) and 86 normal weight individuals (BMI = 18.5 to 24.9 kg/m²) were genotyped for 385 C/A polymorphism of FAAH using amplification refractory mutation system (ARMS)-PCR. Anthropometric indices including BMI, waist circumference, neck circumference, waist to height ratio, fat mass were evaluated. A written informed consent form was given by the participants. The genotype and allele frequencies were significantly different between the overweight/obese and control groups (P = 0.04). Significant differences were observed between the CC genotype and the AA+CA genotype regarding the anthropometric indices (P < 0.05). Compared to CC group, a higher BMI, WC, WHR, NC and fat mass was identified in allele A carriers group. After adjusting for age, marital and physical activity status, it was revealed that having the CA/AA genotype increased the probability of obesity risk almost two times (P < 0.05, 95% CI 1.19–3.67). Our findings showed that the frequency of A allele was greater in overweight/obese individuals. Also, a mutation in FAAH gene was associated with higher anthropometric indices and the CA/AA genotype increased significantly the possibility of being obese in Iranian women.

Keywords Obesity · Endocannabinoids · Polymorphism · Fatty acid amide hydrolase

Introduction
Obesity has become one of the most important health challenges in the last decades and its prevalence is worsening throughout the world [1]. It is projected that if secular trends continue, approximately 38% of the world’s adult population will be overweight and 20% will be obese by 2030 [2]. Comparable to the developed countries, in developing countries the obesity rate has also tripled during the past years [3]. Iran is also one of the developing countries in which the obesity rate has elevated at an alarming speed and approximately 23.3% of the Iranian adults are obese [4]. Obesity provokes or exacerbates a number of pathologies alone or in conjunction with other health issues [5, 6]. Obesity mainly accounts for the incidence of several chronic diseases including cardiovascular disease, type two diabetes, and different types of cancers [7–9].

In addition to the role of environmental factors in overweight and obesity spread, previous reports has repeatedly
emphasized that genetic factors play significant role in several adiposity traits, such as BMI, waist circumference, visceral and subcutaneous adipose tissue, and etc. [10–12]. It is believed that genetic factors and polymorphisms in related genes are currently responsible for 40–70% of the variance in human adiposity [13]. In the last few decades, the genes and molecules which are responsible for energy intake regulation have been spotted and studied widely [14–16].

Endogenous cannabinoids are lipid molecules produced from phospholipids or triglycerides of the membrane with several effects on metabolic regulation and body weight [17]. Different enzymes get involved in the synthesis and degradation of the two most significant endocannabinoids, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) [18]. Fatty acid amide hydrolase (FAAH) has been known as the key catabolic enzyme, capable of deactivating most of the endocannabinoids including AEA [19]. FAAH is a serine hydrolase and a missense c.385C>A single-nucleotide polymorphism (SNP) (rs324420) in the human FAAH gene replaces a conserved proline residue at amino acid position 129 to threonine [20]. This replacement can lead to a decrease in FAAH expression or activity, resulting in continued stimulation of the cannabinoid 1 receptor through the increased levels of the endogenous fatty acid amides which in turn increase appetite, food intake and body fat accumulation [21].

Although genetic variation in FAAH particularly the homozygous FAAH 385 A/A genotype has formerly been shown to be associated with overweight and obesity [22–24], others have failed to find such association [25, 26]. Additionally, there is scarcity of studies about the relation of FAAH gene polymorphisms with obese phenotypes in the Asian population. To this end, since determining of the common genetic variants that affect obesity risk at a population level might improve the pathophysiologic conception of obesity, this study was designed to evaluate the FAAH gene polymorphisms status and to compare the obesity indices between different genotypes in Iranian overweight/obese women.

**Subjects and methods**

**Participants and study design**

This cross-sectional study was carried out between October 2017 and January 2018. The study protocol was approved by local ethical committee (IR.TBZMED.REC.1396.620) and all the participants consented to use their genetic material and other necessary information. A total of 180 healthy overweight/obese subjects (BMI = 25 to 40 kg/m²) and 86 normal weight individuals (BMI = 18.5 to 24.9 kg/m²) were enrolled in this study and all the participants were collected from the same geographical area. Since the obesity rate and food craving is more prevalent among women, we carried out this research only among women. Those having history of any metabolic disorders such as diabetes, kidney and liver disease as well as pregnant and lactating women were excluded. The demographic and physical activity information of the participants was recorded using the appropriate questionnaire by trained dietitian. The individuals’ physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ).

**Anthropometric and body composition**

The measurement of anthropometric indices including weight, height, waist circumference (WC), neck circumference (NC), and blood pressure were carried out in line with standard protocols in fasting state [27, 28]. By dividing WC by height the waist-to-height ratio (WHtR) was determined. BMI was calculated as weight (kg) divided by the square of the height (m²). Fat mass was evaluated by bioelectrical impedance analysis (BC-418MA, Tanita, Japan).

**DNA extraction and genotyping**

Fasting venous blood samples were collected for genotyping process. The genomic DNA extraction from peripheral blood cell was carried out using DNA extraction and purification kit (Qiagen, Cat No./ID: 51306) as manufacturer’s protocol. Optical density measurement (quantitative method based) was used to determine the genomic DNA concentration. By calculating the absorbance ratio at 260 nm to absorbance at 280 nm (A260/A280) the samples purity was confirmed. The genotyping was carried out by the amplification refractory mutation system (ARMS)-PCR in which sequence-specific PCR primers allows amplification of test DNA only when the target allele is within the sample. The forward common primer 5′-GCCAGAGACAGCCAGGATGAGG-3′ and reverse primer 5′-ATAGAGCGGCTGGCCTTG-3′ were used to amplify a 314 bp product to detect the wild types. Also, the forward common primer 5′-GCCAGAGACAGCCAGGATGAGG-3′ together with reverse primer 5′-ATAGAGCGGCTGGCCTTG-3′ were used to amplify and detect 314 bp mutant forms. Moreover, to confirm the accuracy of PCR results and to spot any negative results on agarose gel Hemoglobin (Hb) primers with the following sequences were used as internal controls (110 bp). Hb Forward: 5′-ACACAAGTGTGTCTACTG-3′, Hb Reverse: 5′-CACTTGTCCAGTGTCC-3′ Fig. 1. The PCR reaction was performed in a total reaction volume of 30 µl as previously described [11]. The optimization was carried out and thermo cycler conditions were as follows: the initial denaturation at 96 °C for 5 min followed by 35 cycles of amplification, each cycle consisting of 30 s
at 96°C, 62 s at 30°C and 45 s at 72°C, in a peqlab PCR system. The reaction completed with a one more 7 min of extension at 72°C. PCR products were electrophoresed on 1% agarose gel containing 5 μl/dl safe stain (Cinna Gen Co., Iran). Hardy–Weinberg equilibrium was evaluated.

**Statistical analysis**

Data were analyzed using SPSS software, version 21.0 (IBM Corp., Armonk, NY, USA). Normality of the data distribution was checked by the Kolmogorov–Smirnov goodness-of-fit test. Values are presented as mean ± SD for variables with normal distribution or median (25th; 75th percentiles) for variables without normal distribution. The chi-square test and Fisher’s exact test were used to compare the FAAH 385 C/A genotypes between overweight/obese group as group 1 and control group as group 2. Two-tailed Student’s t test and Mann–Whitney U-test was used to analyze the quantitative variables with normal distribution and nonparametric variables respectively. To predict the association of SNP with the risk of obesity logistic regression model was performed. In all statistical analyses except for Fisher’s exact test, the C358A together with A358A were considered as a first group and wild type C358C as second group. To test the deviation of the observed genotype frequencies from the Hardy–Weinberg equilibrium (HWE), the Chi squared test was used in the overweight/obese and control samples. P value < 0.05 was regarded as statistically significant.

**Results**

The participants’ demographic, anthropometric, and laboratory data are presented in Table 1. The study included 180 overweight/obese (mean age 34.2 ± 8.27 years old; 133 obese, 47 overweight) and 86 normal weight healthy women (mean age 33.1 years old ± 7.03). To test whether FAAH 385 C/A genotypes frequencies differ between overweight/obese and control group chi-square test and Fisher’s exact test were used. As presented in Table 2 the genotype and allele frequencies were significantly different between the overweight/obese and control groups (P = 0.04, fisher exact test). Compared to normal weight women, a greater distribution of the CA (n = 70) and AA (n = 6) genotypes and a lower
distribution of the CC (n = 104) genotype was observed in overweight/obese group. Significant differences were observed between the homozygous genotype AA together with CA and wild homozygous CC regarding the anthropometric indices including BMI, WC, WHtR, NC and fat mass (P < 0.05) (Table 3). In comparison to CC group, a higher BMI, WC, WHtR, NC and fat mass was identified in allele A careers group for the polymorphism 385C>A in FAAH. With respect to the logestic regression analysis, after adjusting for age, marital and physical activity status it was revealed that having the CA/AA genotype increased the probability obesity risk almost two times (P < 0.05, OR 2.28 95% CI 1.19–3.67) (Table 4). In overweight/obese group, the 54.4% of the individuals had low levels of activity, 39.4% were moderately active and the rest of them were highly active (6.1%). Similarly, in normal weight participants, the 94.2% of the subjects had low levels of activity, 3.5% and 2.3% of them had moderate and high levels of activity respectively. The distribution of the FAAH cDNA 385C to A genotypes in both overweight/obese women (P > 0.05) and healthy controls (P > 0.05) did not deviate from HWE.

Discussion

The chronic over-activation of the endogenously produced cannabinoids in obesity has been demonstrated in several studies [29–31]. A common 385C>A single nucleotide polymorphism (SNP) of the FAAH, one the most important degrading enzymes of endocannabinoids, leads to a missense mutation making a FAAH with defective expression [32].

Present study indicated that the minor 385A allele was more usual in the overweight/obese patients compared to normal weight women. In overweight/obese individuals, the AA genotype percentage (3.3%) was comparable with other studies, for instance; 3.7% [22], 2.3% [26], and 1% [24]. Also, the CA genotype percentage (38.89%) was almost identical with other papers; 24.1% [22], 28.1% [26], and 36.5% [24]. The A allele of FAAH cDNA 385C to A SNP was also associated with a significant risk to develop obesity (OR 2.28, 95% CI 1.19–3.67). Moreover, BMI, WC, WHtR, NC and fat mass was higher in CA+AA group compared to individuals with CC genotypes.

The association of FAAH gene polymorphism and mutant allele carriers with obese phenotypes has been investigated in previous studies which yield contradictory results. In a study by Chiang et al. in 2004, it was reported that FAAH enzymatic activity and protein expression in FAAH 385 A/A missense polymorphism individuals was almost half of the wild-type subjects [33]. Also, the CA genotype percentage (38.89%) was almost identical with other papers; 24.1% [22], 28.1% [26], and 36.5% [24]. The A allele of FAAH cDNA 385C to A SNP was also associated with a significant risk to develop obesity (OR 2.28, 95% CI 1.19–3.67). Moreover, BMI, WC, WHtR, NC and fat mass was higher in CA+AA group compared to individuals with CC genotypes.

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Minor A allele carrier [34]. However, in a 5801 of Danish population, no association existed between the FAAH A allele and BMI, WHR, WC, HOMA-IR [25]. Interestingly, there were other studies which revealed that the A allele has been associated with lower blood pressure, with improved cardiovascular profile and larger reduction in glucose, LDL, BMI, WC, triglycerides and total cholesterol under low fat and hypocaloric diet [35].

According to the evidence, half of the FAAH enzymatic activity and protein expression has been seen in minor A allele carriers in comparison to wild-type subjects leading to considerably elevated levels of AEA [36]. In a study by Sipe et al. carried out on 48 normal weight subjects (BMI of ≤26 kg/m²) and 96 severe obese individuals (BMI of ≥40 kg/m²) significant elevation of AEA levels and similar substances in carriers of the FAAH 385 A mutant alleles were identified [22]. In another study, Martins et al. reported a remarkable association between increased AEA levels and the AA homozygous genotype in a multiethnic Brazilian population with a broad range of adiposity values [37]. We also noticed that AEA and 2-AG levels correlated positively with obesity indices including BMI, WC and BF% (data are not shown). Likewise, compared with their wild-type littermates, FAAH/−/− mice exhibited increased energy storage [38]. AEA is one of the main endocannabinoids which can stimulate the CB1 receptor and has the capability of arousing appetite and feeding behavior which ultimately might promote the diet-induced obesity [39]. Additionally, the FAAH A385A could trigger the up regulation of natural reward behaviors such as palatable and sweets food consumption related to overweight and obesity. Indeed, the anatomical intersection of CB1 receptors and FAAH enzyme supports the view that FAAH is placed for endocannabinoid levels regulation that could affect craving and reward behaviors over the pertinent neuronal circuitry and eventually the promotion of energy storage [40].

However, the discrepancies seen in different studies regarding the association of FAAH gene polymorphism with obese phenotype might stem from the fact that further gene–gene or gene–environment interactions are responsible in the obesity appearance and metabolic abnormalities and polymorphisms are not the sole contributing factors.

In summary, the frequency of A allele was greater in overweight/obese individual and mutation in FAAH gene was associated with higher anthropometric indices in Iranian women. This study provides additional support for peripheral endocannabinoid system role in obesity and associated comorbidities which could possibly help to detect the subjects with a genetic susceptibility to obesity whom might gain advantage from primary prevention approaches. However, to improve the precision of our study, larger samples and further information about the metabolic and environmental factors which control the FAAH gene expression is required.

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