C358A Polymorphism of the Endocannabinoid Degrading Enzyme Fatty Acid Amide Hydrolase (FAAH) Influence On Metabolic Parameters a High Protein/Low Carbohydrate versus a Standard Hypocaloric Diet

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Abstract

**Background and aim:** The C358A polymorphism of FAAH gene (rs324420C>A) has been associated with obesity. We investigate the role of this polymorphism on cardiovascular risk factors and weight loss secondary to a high protein/low carbohydrate vs. a standard hypocaloric diets (1000 kcal/day) during 9 months.

**Methods:** A sample of 284 subjects with obesity (body mass index (BMI) >30) was enrolled. These subjects were randomly allocated to one of two diets for a period of nine months Diet S (standard protein hypocaloric diet) vs. Diet HP (high protein-low carbohydrate hypocaloric diet).

**Results:** After both diets and in both genotype groups (CC vs. CA+AA), body mass index (BMI), weight, fat mass, waist circumference and systolic blood pressure decreased. With the diet type HP and in non A carriers, glucose (-5.3 ± 1.2 mg/dl vs. -1.8 ± 2.1 mg/dl; p<0.05), insulin levels (-3.1 ± 1.9 UI/L vs. -1.1 ± 2.0 UI/L; p<0.05), HOMA-R (-0.9 ± 0.8 units vs. -0.3 ± 1.0 units; p<0.05), total cholesterol (-11.9 ± 8.2 mg/dl vs. -0.1 ± 3.1 mg/dl; p<0.05), and LDL- total cholesterol (-9.8 ± 4.2 mg/dl vs. -1.0 ± 2.1 mg/dl; p<0.05) decreased. After diet S and in patients with both genotypes, total cholesterol (-6.0 ± 3.1 mg/dl vs. -10.0 ± 8.2 mg/dl; ns), triglycerides (-8.1 ± 7.1 mg/dl vs. -13.1 ± 8.9 mg/dl; ns) and LDL- total cholesterol (-5.9 ± 3.0 mg/dl vs. -9.1 ± 5.8 mg/dl; p<0.05) decreased.

**Conclusion:** Non carriers of the allele A385 of FAAH showed an improvement on insulin and HOMA-R levels with a high protein hypocaloric diet after weight loss during 9 months. A standard hypocaloric diet produced a similar improvement in lipid profile in both genotypes.

Keywords: FAAH; Hypocaloric diet; Metabolic parameters; Polymorphism

Abbreviations: BMI: Body Mass Index; HOMA-R: Homeostasis Model Assessment; IR: Insulin Resistance; WC: Waist Circumference; FFMI: Fat Free Mass; FM: Fat mass; WHR: Waist to hip ratio; SBP: Systolic Blood pressure; DBP: Diastolic blood pressure

Introduction

Obesity is major public health problems that are estimated to affect >50% of the population and have been linked as risk factors for many common diseases [1]. One of the pathways related with obesity is the endocannabinoid system, which is involved in the control of food intake and body weight. This endocannabinoid system comprises of a number of proteins involved in endocannabinoid synthesis, degradation, and signaling and has been demonstrated to play a role in appetite and body weight, as above mentioned [2]. One of these proteins is Fatty acid amide hydrolase (FAAH), this enzyme inactive the orexigenic effect of the endocannabinoid N-arachidonoylthanolamine (anandamide) by a rapid hydrolysis to ethanolamine and arachidonic acid [3].

One polymorphism of this enzyme (cDNA 385 C->A) (rs324420) has been described [4]. SNPs are estimated to participate in 90% of the disparities between individuals and consist in a replacement in a single nitrogenous base that occurs in at least 1% of population [5]. Some of these SNPs may affect the synthesis and functions of proteins and, therefore, may alter the nutritional requirements and nutrient metabolism [6,7], as well as elicit important roles in individual’s risk of developing diseases [8]. Some studies have shown an interaction between this polymorphism and the metabolic response after weight loss secondary to different hypocaloric diets [9-11]. Perhaps, the percentage of macronutrients in these hypocaloric diets and the type of dietary fat may influence the heterogeneous metabolic responses secondary to weight loss as a function of this polymorphism. A recent meta-analysis of clinical trials with low-carbohydrate/high protein diets has shown that such diets have favorable effects on weight reduction and other major cardiovascular risk factors [12]. As far as we know, no studies have evaluated the effect of this polymorphism on response to diets of this type.

In attempting to understand the role of (rs324420) variant of Fatty acid amide hydrolase in obese patients, we decide to investigate the role of this polymorphism on cardiovascular risk factors and weight loss secondary to a high protein/low carbohydrate vs. a standard hypocaloric diets (1000 kcal/day) during 9 months.

Subjects and Methods

**Subjects**

A sample of 284 subjects (75 males/209 females) with obesity (body mass index (BMI) >30) was enrolled in a prospective way. These subjects

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were randomly allocated to one of two diets for a period of nine months. Diet S (standard protein hypocaloric diet) vs. Diet HP (high protein-low carbohydrate hypocaloric diet). Local ethical committee (CEIC-HURH) approved the protocol (4-2014 CEIC HURH) and patients approved the use of their genetic material for this study. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. All patients were recruited in a Nutrition Clinic Unit and signed an informed consent. Exclusion criteria included: total cholesterol > 300 mg/dl, triglycerides > 300 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose >110 mg/dl, as well as the use of drugs with potential metabolic effects as statins, fibrates, metformin, sulphonylurea, thiazolidinediones, insulin, glucocorticoids, antineoplastic agents, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and psychoactive medications.

Procedures and dietary intervention
Weight, height, body mass index, fat mass (bioimpedance), waist circumference, blood pressure, basal glucose, c-reactive protein (CRP), insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and blood adypkines (leptin, adiponectin and resistin) levels were measured within the start of the trial and repeated after 3 months and 9 months of both dietary intervention. 284 obese subjects were randomly allocated to one of two diets for a period of nine months. Diet S (standard protein hypocaloric diet) consisted in a diet of 1093 cal/day, 53% carbohydrates (144.3 g/day), 27% fats (32.6 g), and 20% proteins (55.6 g/day). The distribution of fats was; 20.9% of saturated fats, 67.4% of monounsaturated fats and 11.6% of polyunsaturated fats. Diet HP (high protein-low carbohydrate hypocaloric diet) consisted in a diet of 1050 cal/day, 33% of carbohydrates (86.1 g/day), 33% of fats (39.0 g/day) and 34% of proteins (88.6 g/day). The distribution of fats was; 23.5% of saturated fats, 63.8% of monounsaturated fats and 12.6% of polyunsaturated fats. The exercise program consisted of an aerobic exercise at least 3 times per week (60 min each). The adherence of these diets was assessed each 7 days with a phone call by a dietitian in order to improve compliment of the calorie restriction and macronutrient distribution. National composition food tables were used as reference [13].

Genotyping of FAAH gene polymorphism
Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International®, LA, CA). The polymerase chain reaction (PCR) was carried out with 50 ng of genomic DNA, 0.5 uL of each oligonucleotide primer (primer forward: 5'-ATG TTG CTG GGT ACC CCT CCT C -3'; primer reverse: 5'-CAG GGA CGC CAT AGA GCT G-3') and 0.25 uL of each probes (wild probe: 5'-Fam-CTG TCT CAG GCC CCA AGG CAG G-BHQ-1-3' and (mutant probe: 5'-Hex-CTG TCT CAG GCC ACA AGG CAG G -BHQ-1-3') in a 25 uL final volume (Termociclador iCycler IQ (Bio-Rad®, Hercules, CA)). DNA was denaturized at 95°C for 3 min; this was followed by 50 cycles of denaturation at 95°C for 15 s, and annealing at 59.3°C for 45 s. The PCR were run in a 25 uL final volume containing 12.5 uL of IQTM Supermix (Bio-Rad®, Hercules, CA) with hot start Taq DNA polymerase. Hardy Weinberg equilibrium was assessed.

Assays
Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, California), coefficients of variation of intra-assay (IACV) (1.5%) and inter-assay (IECV) (2.1%). Insulin was measured by RIA (RIA Diagnostic Corporation, Los Angeles, CA) with a sensitivity of 0.5mUI/L (normal range 0.5-30 mUI/L), coefficients of variation of intra-assay (IACV) (1.8%) and inter-assay (IECV) (2.5%) [14], and the homeostasis model assessment for insulin resistance (HOMA-R) were calculated using these values [15]. CRP was measured by immunoturbimetry (Roche Diagnostics GmbH, Mannheim, Germany), with a normal range of (0-7 mg/dl) and analytical sensitivity 0.5 mg/dl with a coefficients of variation of intra-assay (IACV) (2.1%) and inter-assay (IECV) (2.3 Plasma hormone levels were evaluated using the multiplex Biorad® 10plex assay following manufacturer's instructions (Bio-Rad®, Hercules, CA). This system allows for quantitative measurement of different hormones, while consuming a small amount of biological material; resistin, leptin and adiponectin. Limits of detection were as follows (pg/ml): leptin (1.8), resistin (1.4) and adiponectin (3.8).

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL cholesterol was calculated using Friedewald formula [16].

Anthropometric measurements and blood pressure
Body weight was measured to an accuracy of 0.1 Kg and body mass index computed as body weight/(height²). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to hip ratio (WHR) were measured, too. Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer and a large cuff size was, and averaged. Tetrapolar body electrical bioimpedance (EFG, Akern, It) was used to determine body composition with an accuracy of 50 g [17]. Resistance and reactance were used to calculate total body water, fat and fat-free mass. The same investigator measured patients. Precautions taken to insure valid BIA measurements were; no alcohol within 24 hours of taking the test, no exercise or food for four hours before taking the test.

Statistical analysis
Sample size was calculated to detect differences over 3 kg in body weight with 90% power and 5% significance (n=140 in each dietary intervention). The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables were analyzed with a 2-way ANOVA model with genotype as the intergroup factor and intervention as the intragroup intervention. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher’s test. A Chi square test was used to evaluate the Hardy–Weinberg equilibrium. The statistical analysis was performed for the combined C385A and A385A as a group and C385C as second group (dominant model). A p-value under 0.05 was considered statistically significant.

Results
Two hundred and eighty four patients gave informed consent and were enrolled in the study. The mean age was 50.2 ± 10.2 years and the mean BMI 35.0 ± 3.4, with 75 males (26.4%) and 209 females (73.6%). One hundred and ninety seven patients (48 males/149 females) (69.4%) had the genotype CC, 280 (97.6%) had the genotype CC, and 87 (30.7%) patients (27 males/60 females) CA (n=84, 29.6%) or AA (n=3, 1.1%) (A allele carriers). The Hardy Weinberg equilibrium was fulfilled p=0.37. Sex distribution was similar in groups, males (24.4% vs. 30.1%) and females (75.6% vs. 69.9%). Age was similar in both groups (CC genotype: 51.1 ± 10.1 years vs. A carriers group: 49.9 ± 12.8 years: ns).
Anthropometric characteristics of participants at baseline and at 3-9 months of intervention are shown in Table 1. With the diet type HP (high protein hypocaloric diet) and in both genotype groups (CC vs. CA+AA), body mass index (BMI) (-2.4 ± 1.0 kg/m² vs. -2.3 ± 1.3 kg/m²; ns), weight (-7.4 ± 2.1 kg vs. -8.1 ± 4.2 kg; ns), fat mass (-5.4 ± 3.0 kg vs. -5.9 ± 3.1 kg; ns), waist circumference (-7.4 ± 5.1 cm vs. -7.9 ± 4.5 cm; ns) and systolic blood pressure (-4.2 ± 2.1 mmHg vs. -4.9 ± 1.9 mmHg;ns) decreased. There were not significant differences between the effects (on weight, BMI, waist circumference, systolic blood pressure and fat mass) in either genotype group. With the diet type S (Standard hypocaloric diet) and in both genotypes, BMI (-2.9 ± 1.1 kg/m² vs. -2.0 ± 1.0 kg/m²;ns), weight (-9.6 ± 5.0 kg vs. -6.8 ± 3.9 kg;ns), fat mass (-6.2 ± 3.2 kg vs. -5.1 ± 3.1 kg;ns), systolic blood pressure (-6.0 ± 1.1 mmHg vs. -5.9 ± 1.8 mmHg;ns) and waist circumference (-7.5 ± 4.1 cm vs. -7.1 ± 3.8 cm;ns) decreased. There were no significant differences between the effects in either genotype group with diet S. The effects of both diets on weight, BMI, waist circumference, systolic blood pressure and fat mass were similar.

In the 140 subjects (97 CC genotype and 43 A allele carriers) treated with diet HP, basal assessment of nutritional intake with a 3 days written food record showed a basal calorie intake of 2009.2 ± 196.1 kcal/day, a carbohydrate intake of 213.3 ± 20.9 g/day (40.9% of calories), a fat intake of 90.1 ± 23.1 g/day (41.0% of calories) and a protein intake of 80.8 ± 32.3 g/day (27.1% of calories and 37.1% of proteins). The 144 subjects (100 CC genotype and 44 A allele carriers) treated with diet S, basal assessment of nutritional intake with a 3 days written food record showed a basal calorie intake a calorie intake of 2018.2 ± 321.9 kcal/day, a carbohydrate intake of 213.8 ± 21.2 g/day (42.9% of calories), a fat intake of 90.0 ± 11.1 g/day (38.3% of calories) and a protein intake of 89.9 ± 10.9 g/day (19.8% of calories). During the intervention, these patients reached the recommendations of diet; 1013.1 ± 92.1 kcal/day (51.6% of carbohydrates, 29.5% of lipids and 18.9% of proteins).

Table 2 shows the cardiovascular risk factors. With the diet type HP and in non A carriers, glucose (-5.3 ± 1.2 mg/dl vs. -1.8 ± 2.1 mg/dl; p<0.05), insulin levels (-3.1 ± 1.9 UI/L vs. -1.1 ± 2.0 UI/L; p<0.05), HOMA-R (-0.9 ± 0.8 units vs. -0.3 ± 1.0 units; p<0.05), total cholesterol (-11.9 ± 8.2 mg/dl vs. -0.1 ± 3.1 mg/dl; p<0.05), and LDL- total cholesterol (-9.8 ± 4.2 mg/dl vs. -1.0 ± 2.1 mg/dl; p<0.05) decreased. All these parameters remained unchanged in patients with A allele. With the diet S and in patients with both genotypes, total cholesterol (-6.0 ± 3.1 mg/dl vs. -10.0 ± 8.2mg/dl;ns), triglycerides (-8.1 ± 7.1 mg/dl vs. -13.1 ± 8.9 mg/dl;ns) and LDL- total cholesterol (-5.9 ± 3.0 mg/dl vs. -9.1 ± 5.8mg/dl; p<0.05) decreased.

Table 3 shows levels of adipocytokines. With the diet HP and in both genotypes, leptin levels (-16.9 ± 9.1 ng/ml vs. -19.4 ± 11.0 ng/ml;ns) decreased. With the diet S, leptin levels (-18.5 ± 5.3 ng/ml vs. -20.1 ± 4.9 ng/ml;ns) decreased in both genotypes, too. The amount of leptin decrease was similar with both diets. Adiponectin and resistin levels remained unchanged after both diets in all groups.

Table 1: Changes in Anthropometric Variables (Mean ± S.D.)

| Characteristics | CC(n=97) | CA+AA(n=43) | CC(n=100) | CA+AA(n=44) |
|-----------------|---------|------------|-----------|-------------|
| BMI (kg/m²)     | 34.8 ± 5.1 | 33.7 ± 4.1 | 34.1 ± 4.4 | 33.7 ± 4.4 |
| Weight (kg)     | 91.7 ± 17.6 | 86.5 ± 13.0 | 92.1 ± 17.4 | 87.8 ± 12.1 |
| Fat mass (kg)   | 36.3 ± 7.0 | 32.9 ± 7.2 | 35.1 ± 11.1 | 31.8 ± 10.1 |
| WC (cm)         | 111.8 ± 12 | 106.0 ± 10.7 | 114.2 ± 9.2 | 107.4 ± 9.1 |
| WHR             | 0.95 ± 0.07 | 0.92 ± 0.06 | 0.97 ± 0.01 | 0.95 ± 0.01 |
| SBP (mmHg)      | 122.7 ± 11.8 | 123.1 ± 10.9 | 129.7 ± 11.4 | 124.1 ± 10.2 |
| DBP (mmHg)      | 82.1 ± 10.5 | 79.5 ± 8.1 | 82.2 ± 8.1 | 82.7 ± 9.0 |

Table 2: Changes in Cardiovascular Risk Factors (Mean ± S.D.)

| Characteristics | DIET HP (n=140) | CA+AA (n=43) | DIET S (n=144) | CA+AA (n=44) |
|-----------------|-----------------|--------------|----------------|--------------|
| Glucose (mg/dl) | 104.6 ± 9.2     | 99.2 ± 11.1 | 104.5 ± 12.2   | 101.5 ± 9.1  |
| Total chol. (mg/dl) | 209.4 ± 20.8 | 196.1 ± 20.1 | 203.4 ± 21.7   | 204.7 ± 30.0 |
| LDL-chol. (mg/dl) | 131.8 ± 20.2 | 120.3 ± 20.1 | 126.6 ± 21.2   | 127.4 ± 20.1 |
| HDL-chol. (mg/dl) | 55.3 ± 10.5 | 54.7 ± 9.1 | 56.6 ± 10.9    | 56.3 ± 8.2   |
| TG (mg/dl)      | 128.3 ± 49.1   | 112.3 ± 31.4 | 107.2 ± 21.2   | 106.6 ± 30.1 |
| Insulin (mUI/L) | 11.6 ± 5.4     | 8.9 ± 5.1    | 10.8 ± 7.0     | 8.8 ± 7.1    |
| HOMA             | 2.4 ± 0.9      | 2.0 ± 1.1    | 2.8 ± 1.0      | 2.4 ± 1.3    |
| CRP (mg/dl)     | 5.0 ± 3.1      | 4.4 ± 3.2    | 4.0 ± 3.1      | 4.9 ± 3.2    |
Discussion

The main finding of our study is the association of the C385C genotype with an additional improvement in lipid profile, glucose, insulin, and HOMA-R levels after a high protein hypocaloric diet. A standard hypocaloric diet produced a similar improvement in lipid profile in both genotypes. A significant decrease of weight, fat mass, waist circumference, total cholesterol and LDL-cholesterol were observed in subjects with both diets in all genotype groups. These relevant data are interesting because there are few intervention studies in this topic area. Five studies reported that carriers of the A allele of rs324420 had different changes in several biochemical parameters after weight loss secondary to a dietary intervention. Aberle et al. [9] have shown that carriers of the A allele had a significantly greater improvement in cholesterol profile compared to non-carriers of A allele when following a low fat diet during a short intervention trial of 6 weeks. De Luis et al. [10] have shown with a standard hypocaloric diet during 3 months (52% of carbohydrates, 25% of lipids and 23% of proteins) that carriers of the A allele was associated with higher improvements in HDL cholesterol and glucose levels than non A allele carriers. In other study with two branches of intervention of 12 weeks [11], the allele A385 of FAAH was associated with a lack of improvement on metabolic parameters after a low fat hypocaloric diet and a low carbohydrate hypocaloric diet. However, in this study [11], the type of diet interacts with the genotype and the low fat diet produce a significant decrease of glucose, HOMA-R, and insulin levels. The type of dietary fat in hypocaloric diet has shown a relevant role in the metabolic response. For example, in a study during 3 months with a high monounsaturated hypocaloric diet [18], subjects with C385C genotype had a significant improvement on insulin and HOMA-R levels and a low carbohydrate hypocaloric diet after weight loss during 9 months. A standard hypocaloric diet produced a similar improvement in lipid profile in both genotypes. Further studies are needed to explore the right macronutrient distribution and type of dietary fats to evaluate this interaction gene-environment.

Table 3: Circulating Adipocytokines (Mean ± S.D.)

| Characteristics       | CC(n=97)  | CA+AA(n=43) | CC(n=100) | CA+AA(n=44) |
|-----------------------|-----------|-------------|-----------|-------------|
| Adiponectin (ng/ml)   | 10.1 ± 6.0| 9.7 ± 5.2   | 10.0 ± 7.0| 9.2 ± 5.0   |
|                       | 10.2 ± 5.0| 11.0 ± 9.1  | 10.8 ± 7.3| 11.1 ± 4.0  |
|                       | At 3 mths | At 9 mths   | At 3 mths | At 9 mths   |
| Resistin (ng/ml)      | 7.1 ± 3.0 | 7.0 ± 5.0   | 6.9 ± 4.8 | 7.3 ± 3.1   |
|                       | 7.1 ± 3.1 | 7.2 ± 3.3   | 8.0 ± 2.5 | 7.9 ± 3.1   |
|                       | At 9 mths | At 15 mths  | At 9 mths | At 15 mths  |
| Leptin (ng/ml)        | 31.8 ± 17.4| 21.9 ± 13.1*| 30.1 ± 10.1| 20.1 ± 9.0* |
|                       | 18.4 ± 9.1*| 33.5 ± 12.0  | 20.4 ± 7.0*| 15.0 ± 5.1* |
|                       | At 15 mths| At 30 mths  | At 15 mths| At 30 mths  |

(*) p<0.05, in each group with basal values. No statistical differences between genotypes with CC vs. CA+AA carriers in each diet.

In conclusion, non-carriers of the allele A385 of FAAH showed an improvement on insulin and HOMA-R levels with a high protein hypocaloric diet after weight loss during 9 months. A standard hypocaloric diet produced a similar improvement in lipid profile in both genotypes. Secondary weight loss after diet was similar in both genotypes. Further studies are needed to explore the right macronutrient distribution and type of dietary fats to evaluate this interaction gene-environment.

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D. A de Luis designed the study and wrote the article, R. Aller recruited patients, made dietary evaluation and wrote the article, E Romero realized laboratory test, O Izalo recruited patients and made dietary evaluation, R Bachiller recruited patients and made dietary evaluation.

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