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Racial and sex differences in the polymorphisms of the endocannabinoid receptor genes in obesity

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Abstract

Background: Obesity is a global epidemic and prevalence of obesity is higher in African Americans (AAs) compared to Caucasians. The endocannabinoid system (EC) and polymorphims in the endocannabinoid receptor type 1 (CNR1) gene 3813A/G and 4895A/G and in the fatty acid amide hydrolase (FAAH) are associated with obesity. The objective was to explore racial and sex differences in these polymorphims and the biochemical abnormalities seen in obesity.

Methods: A cross-sectional study of 667 subjects (53.67% female, 49.18% were AA; 69.72% were obese (body mass index [BMI] ≥30) were screened for CNR1 3813, 4895 and FAAH 385 polymorphisms using a real-time polymerase chain reaction (PCR) system.

Results: Subjects with FAAH 385 polymorphisms were more likely to be obese (75.14% vs. 67.81, *P*=0.046). There were no significant sex differences for CNR1 3813 and CNR1 4895; or between obese and control group. AAs had higher prevalence of CNR1 3813 (OR, 2.80, 95% CI,

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1.95 – 4.04) and FAAH 385 (OR, 2.48, 95% CI, 1.82–3.38). Association between African American race and the three genotypes persisted after adjustment of all the variables ($P<0.001$).

Conclusion: FAAH 385 polymorphism is more likely seen in obese and in older subjects. AAs had higher prevalence of CNR1 3813 and FAAH 385 polymorphims; and lower prevalence of CNR1 4895 polymorphisms. These findings may explain some of the racial differences, but not the sex differences in the clinical expression of obesity.

Keywords

endocannabinoid receptors genes; CNR1; fatty acid amide hydrolase; FAAH; polymorphisms; obesity; diabetes mellitus

Introduction

Obesity has led to an epidemic of diabetes, cardiovascular disease, and other obesity-related problems. African-Americans (AA) have a higher prevalence of obesity as compared to Caucasians.[1] AAs also have a higher prevalence of hypertension and type 2 diabetes mellitus (T2DM).[2] The Bogalusa Heart Study[3] is a long-term community based investigation of cardiovascular risk factors in black (35%) and white (65%) children and young adults in Bogalusa, Louisiana. Insulin resistance index was found to be significantly higher in females than in males for both the races. Among the white adults, the insulin resistance index was significantly higher in males as compared to females. Insulin resistance index was also noted to be significantly higher in blacks only in male children, female adolescents and female adults. Whereas, body mass index (BMI) was higher in female adolescents (both black and white) and black female adults, but was lower in white female adults. The reason(s) behind these differences is not clear.

The endocannabinoid system has been related to adipocyte physiology and obesity.[4,5] This endocannabinoid system consists of two G protein-coupled receptors known as cannabinoid receptors CB1 and CB2; their endogenous ligands, the endocannabinoids; and the enzymes responsible for ligand biosynthesis and degradation. The endocannabinoid system (EC) plays important regulatory roles in the control of food intake, energy balance, and body mass through central and peripheral mechanisms.[6] The two most studied endocannabinoids, 2-arachidonoylglycerol (2-AG) and anandamide or *N*-arachidonoylethanolamine (AEA), increase food intake and promote weight gain in animals by activating central endocannabinoid receptors. CB1 gene-deficient mice are lean and resistant to diet-induced obesity.[7] Selective CB1 blockade has been shown to reduce food intake and body weight in obese animals and humans. The circulating levels of both 2-AG and AEA are higher in obese compared with lean humans.[4,6] Activation of cannabinoid-1 [CB1] receptors in the hypothalamus is thought to be associated with stimulation of appetite, but the CB1 receptors are also present in peripheral adipose tissue and other organs, and they may affect the clinical expression of the obesity problem. Data suggests that CB1 blockage may lead to not only reduction in body weight, but also an improvement in the features of diabetes and the metabolic syndrome.[8]

Single nucleotide polymorphisms (SNPs) of the CNR1, CNR1 4895A/G (rs806368), and CNR1 – 3813A/G (rs12720071) have been associated with obesity.[9] The enzyme fatty acid amide hydrolase [FAAH] is involved in the activation of the endocannabinoid system. Polymorphisms of the gene for the enzyme FAAH, have been shown to be associated with abnormalities[7] in the levels of the endocannabinoids themselves as well as obesity. In one study, polymorphisms in the FAAH enzyme gene are more prominent in people of African-American descent.[10]

Abnormalities in the endocannabinoid system certainly play a prominent role in obesity. There is conflicting data[10–17] about racial differences in these polymorphisms as an explanation for the variation in clinical expression of obesity between AAs and Caucasians. The purpose of this study was to explore racial and sex differences between the CNR1 3813A/G and 4895A/G and the FAAH gene polymorphisms in obese AAs and Caucasians as compared to controls; and to study the relationship of these polymorphisms with some of the biochemical abnormalities seen in obesity such as hyperlipidemia.

Materials and methods

This is a cross sectional single center study that enrolled 667 subjects between November 2008 and June 2012. The study was approved by Tulane University Biomedical the Institutional Review Board (IRB). Subjects were male or female between the ages of 18 – 70. Subjects with BMI ≥ 30 kg/m^2 were assigned in the obese group and those with a BMI ≤27 kg/m^2 were in the control group. Subjects with 27<BMI<30 were not included in the study. Self-reported history of drug abuse and pregnancy was part of the exclusionary criteria. All subjects signed an informed consent form and came in a fasting state for the research visit. History and physical examination was performed and all their medications were noted. During the study visit, blood pressure (BP) was measured and BMI and waist-hip ratio (WHR) were calculated. Venous blood was collected for comprehensive metabolic panel, lipid panel, thyroid stimulating hormone and endocannabinoid genotyping. For those patients that reported a history of DM, hemoglobin A1c (HbA1c) was performed as well.

A fasting blood sample for CNR1 3813A/G and 4895A/G and FAAH C385A polymorphisms genotyping was drawn into EDTA containing tubes. Blood samples were placed on ice and centrifuged immediately within 10 minutes in a refrigerated centrifuge at 1300 xg for 10 minutes. Plasma was then collected from centrifuged blood tubes and snap frozen immediately using liquid nitrogen and stored in −80°C freezer. The time interval between blood sampling and centrifugation was minimized to prevent false positive increases in endocannabinoid plasma concentrations. The buffy coat portion of the samples was collected and stored in −20°C for DNA extraction at a later time using QIAamp DNA Blood kit (QIAGEN Inc. Valencia, CA) and stored at −80°C for genotyping.

Genotyping

Analysis of the Fatty acid amide hydrolase (FAAH) and endocannabinoid receptor type 1 gene (CNR1) polymorphism was performed using a real-time polymerase chain reaction (PCR) by TaqMan allelic discrimination assay. The polymorphic region of FAAH C385A (rs324420), CNR1 4895A/G (rs806368), and CNR1 – 3813A/G (rs12720071) was amplified

in duplicate using TaqMan Genotyping Master Mix (Applied Biosystems, Foster City, CA) in a 7500 Fast Real-Time PCR system (Applied Biosystems, Foster City, CA) and iCycler iQ (Bio-Rad Laboratories Hercules, CA) detection systems. Allelic discrimination calls were determined by the system's software, and 10% of the total sample was re-genotyped to further assure concordance.

Statistical analyses: The presence of each polymorphim was dichotomized as positive (homozygous or heterozygous) or negative (wild-type) for the polymorphim. Numbers and percentages were provided for categorical variables in descriptive analysis including demographic characteristics and medical history. Continuous variables are reported as means and standard deviations, unless noted otherwise. Relevant measures of centrality such as means and medians were presented for continuous measures, as well as variance measures such as standard deviations and percentiles and interquartile range (IQR). Descriptive statistical analysis was compared between the subjects with the presence of polymorphims and those without. Appropriate statistical tests (e.g., t-test, Wilcoxon rank sum test, chi-square test) were used based on the distribution of the measures. Multiple logistic regression model was used to detect association between each of the genotyping and race adjusting for age, sex, obese group, WHR, and LDL-cholesterol (LDL-c) based on our hypotheses and statistical significance in univariate analysis, as well. Because the means of systolic BP and diastolic BP was significantly different between CNR1 3813 polymorphism and CNR1 4813 polymorphism, respectively, additional covariate was added in the model, respectively. The interaction term of race with each covariate was also examined in each model; and a likelihood-ratio test was applied if the interaction term was statistically significant. Tests of statistical significance were based on a 2-tailed type 1 error at $p < 0.05$. All analyses were performed using SAS 9.4.

Results

A total of 667 subjects were evaluated, 465 were obese and 202 were controls with normal BMI. There were 465 subjects in the obese group of whom 251 were AA (male [M]/female [F] = 35/116) and 214 (M/F = 84/130) were Caucasian. The control group had 202 subjects of whom 77 were AA (M/F = 40/37) and 125 were Caucasian (M/F = 50/75). Characteristics of the subjects in the obese and the control groups with the presence of polymorphims and those without the polymorphims are compared within each of the genotypes (i.e. CNR1 3813, CNR1 4895, FAAH 385) (Table 1). Subjects with the FAAH 385 polymorphim were more likely to be obese (OR, 1.40, 95% CI, 1.01–1.96) as compared to those without the FAAH 385 polymorphism; however, the association diminished (adjusted OR, 1.16, 95% CI, 0.76–1.76) when adjusting for age, race, sex, WHR and LDL-c. (Table 2) There were no significant differences in presence of CNR1 3813 or CNR1 4895 polymorphism between obese and control group; nor were there any significant sex differences. The presences of all three polymorphisms were significantly different among racial groups. When compared to Caucasians, the CNR1 3813 polymorphim (OR, 2.80, 95% CI, 1.95 – 4.04) and FAAH 385 polymorphim (OR, 2.29, 95% CI, 1.63–3.21) were more prevalent among AAs. In contrast, the CNR1 4895 polymorphim was less likely to be present in AAs (OR, 0.41, 95% CI, 0.29 – 0.58). No significant age difference was detected among those with and without the

CNR13813 or CNR1 4895 polymorphim. We also found subjects with the CNR1 3813 polymorphim had higher WHR (0.92 ± 0.10 vs. 0.90 ± 0.10, $P = 0.04$) and diastolic BP (80.60 ± 13.54 vs. 77.62 ± 12.25 mm/Hg, $P = 0.008$) than wild type. Subjects with CNR1 4895 polymorphism had lower systolic BP (123.22 ±17.78 vs. 126.76 ± 19.08 mm/Hg, $P = 0.03$) and LDL-c (101.84 ± 30.83 vs. 108.16 ± 34.19 mg/dL, $P = 0.03$). However, these metabolic measurements were no longer associated with any of the CNR1 genotypes in multiple logistic regression models (Table 2). The association between race and each of CNR1 and FAAH polymorphisms was persistent after full adjustments for age, sex, obese group, WHR, LDL-c, systolic and diastolic BP.

Among our study subjects, FAAH polymorphism was detected more often in older patients (47.53 ± 11.84 vs. 44.98 ± 13.24 years, P =0.009) however, this significance diminished after adjustment. (Table 1). The clinical relevance of this statistical significance is not known as a person is born with polymorphism(s) or not. .

Discussion

Our study demonstrated that African American race was associated with polymorphisms of CNR1 3813, CNR1 4895 and FAAH 385. No difference in the distribution of the CNR1 3813 or CNR1 4895 polymorphimss was seen between the obese and the control groups or between males and females. AAs have a significantly higher prevalence of CNR1 3813 and FAAH 385 polymorphimss; whereas the Caucasian subjects had a higher prevalence of CNR1 4895.. Neither CNR1 3813 nor CNR1 4895 were associated with obesity. The prevalence of FAAH 385 was higher in obese subjects, but this association was no longer significant after adjustment for age, race, sex, WHR and LDL-c.

Data from studies done to illustrate the relationship between of the polymorphims of the CNR1 receptor and FAAH among various ethnic groups, at best is conflicting (The new TABLE with the summary of the conflicting results that we've refereced in the paper). In a study by Sipe et[10], European male carriers of the minor A allele of FAAH C385 single nucleotide polymorphism (SNP) were more likely to be obese when compared to normal weight men (n = 1,600; P = 0.004). The same relationship was found in obese men of African descent (n = 614; P = 0.049), similar to our results, however from the same study statistically significant difference in the polymorphism was not found in Asian men.[10] Whereas results from a large population-based study from Denmark that included > 5000 white subjects did not find significant differences in genotypes between lean and overweight/obese white men and women.[11]

Few studies have examined the relationship of the CNR1 and the FAAH polymorphisms with measures of obesity such as BMI, waist circumference, visceral and subcutaneous adipose tissue. Our results show that subjects with the CNR1 3813 polymorphim had higher WHR and diastolic BP as compared to those without the CNR1 3813 polymorphim. Subjects with the CNR1 4895 polymorphism had lower LDL-c and systolic BP levels. These factors were no longer significant when assessed in the logistic regression model. The clinical significance of the BP and the LDL-c association is unclear given that the subjects were taking pharmacologic agents for hypertension and hyperlipidemia.

In the Olivetti Prospective Heart Study (OPHS),[13] the CNR1 3813G (rs12720071, similar to ours) was associated with increased waist circumference ($P = 0.05$) and subscapular skinfold thickness ($P = 0.03$). No association was observed for CNR1 4895A/G with increased waist circumference and subscapular skinfold thickness in the Wandsworth Heart and Stroke Study. In both these studies, the CNR1 4895A/G polymorphism was not associated with BMI, waist circumference or subscapular fold thickness. Lieb et al[12] conducted studied 18 SNPs in the CNR1 gene and 9 SNPs in the FAAH gene in 2,415 Framingham Offspring Study participants. There were unable to find an association of the polymorphisms in the CRN1 and FAAH genes with BMI, waist circumference and visceral or subcutaneous adipose tissue, thus being unable to confirm the relationship of these polymorphisms with obesity.

Inhibition of the CB1 receptor modulates body weight insulin sensitivity[8] and has been associated with improved metabolic profile. It has also been associated with decreased coronary artery total atheroma by coronary intravascular ultrasonography.[18] Study of the 2,411 Framingham participants,[19] with a mean age of 60 years, of which 52% were women, was conducted by genotyping for 19 SNPs of the CNR1. Their results did not yield a reproducible statistically significant association of CNR1 polymorphism with insulin resistance; type 2 DM or coronary heart disease.

The role of the EC system in obesity and the benefits of blockade of the EC system are certainly well established. However, obesity is multifactorial. Polymorphisms of the CNR13813G, 4895A/G and FAAH C385A may very well predispose an individual for weight gain. Longitudinal evidence documenting a temporal relationship between these polymorphisms and the incidence of obesity is however not available. Our study demonstrated that AAs had a higher prevalence of CNR1 3813 and FAAH 385 polymorphisms; whereas Caucasians had a higher prevalence of CNR1 4895A/G. We did not find any sex differences in the prevalence of these polymorphisms. Low prevalence of the polymorphisms in the study subjects resulted in the study being underpowered. The relatively smaller sample size may be a factor, which is a limitation of this study Other studies have also not been able to establish any sex differences in these polymorphisms definitively.

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Appendix

Study	Sample Size	Polymorphisms investigated	Results
Sipe, Waalen, Gerber, & Beutler, 2005	N = 2667 Subjects = White, Black, and Asian	FAAH	Statistically significant differences in presence of the polymorphism in overweight and obese subjects when compared to normal weight for White (p=0.0045) and Black (p=0.0490) subjects. No significant differences among the Asian subjects.
Jensen, Andreasen, Andersen, et al., 2007	N = 5,738 Subjects = White	FAAH	There was a significant difference based on BMI in obese (p=0.03) and overweight/ obese (p=0.04) subjects when compared to normal weight subjects.
Lieb, Manning, Florez, et al., 2009	N= 1,422 Subjects = no race reported	CNR1; FAAH	No significant differences found.
Russo, Strazzullo, Cappuccio, et al., 2007	N= 576Subjects= white males - • 360 from Olivetti Prospective Heart Study and • 216 from Wandsworth Heart and Stroke Study	CNR1 3813 and 4895	OPHS: • CNR1 GG haplotype was significantly associated with higher waist circumference in the 1987 cohort (p=0.004) and 1994–95 follow-up (p=0.021) WHSS: • CNR1 3813 and 4895 polymorphisms were significantly associated with higher waist circumference (p=0.006 and 0.012 respectively). • Only CNR1 3813 was significantly associated with higher BMI (p=0.012) • CNR1 GG haplotype was significantly associated with higher waist circumference (p=0.045) and higher BMI (p=0.033).
Benzinou, Chevre, Ward, et al., 2008	N = total 5210Subjects= • White subjects = 2,105 • Obese subjects = 1,932 • controls = 1,173	CNR1	There were statistically significant associations in polymorphisms A/G and T/C with Class I/II obese adults (p=0.0006 & 0.0004, respectively) and Class III obesity (p=0.01 & 0.07, respectively). Similar results found in the Swiss adults (Class II/III obesity) (p=0.02) and Danish general population (p=0.021), those with the polymorphisms had higher BMIs
Peeters, Beckers, Mertens, & Van Gaal, 2007	N= 1,325Subjects= • Obese = 1,064 • Controls = 251	CNR1	There was no overall significance found in the presence of the polymorphisms when comparing obese subjects and controls. However, in men, higher waist-to-hip ratio (p=0.0009) and waist circumference (p=0.008) were significantly associated with the presence of CNR1 1422 A/A genotype.
Muller, Reichwald, Wermter, et al., 2007	Study Group 1: N = 1,092 Subjects = −Obese 364 children/ adolescents + both biological parents Study Group 2:	CNR1	There was no significant associations between polymorphism and obesity.

Study	Sample Size	Polymorphisms investigated	Results
	N = 501 Subjects = obese children/ adolescents + both biological parents; 253 of 501 included at least 1 obese sibling		

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Highlights

- African American race is associated with polymorphisms of CNR1 3813, CNR1 4895 and FAAH 385.
- No difference in the distribution of the CNR1 3813 or CNR1 4895 mutations was seen between the obese and the control groups or between males and females.
- Among African American subjects aged between 45–54 years and > 55 years that had a higher prevalence of the FAAH polymorphism as compared to subjects between the ages of 18 and 44 years.
- African Americans had a higher prevalence of CNR1 3813 and FAAH 385 polymorphisms; whereas Caucasians had a higher prevalence of CNR1 4895A/G.

Table 1:

Clinical and biochemical characteristics of the subjects in the various groups:

Variable	CNR1 3813 polymorphims		CNR1 4895 polymorphims		FAAH 385 polymorphims		Total (N=667)
	+ (n=173)	− (n=494)	+ (n=193)	− (n=474)	+ (n=323)	− (n=344)	
Obese, n (%)	130 (75.14)	335 (67.81)	132 (68.39)	333 (70.25)	237 (73.37)	228(66.28)*	465 (69.72)
Female, n (%)	86 (49.71)	272 (55.06)	106 (54.92)	252 (53.16)	170 (52.63)	188 (54.65)	358 (53.67)
AA, n (%)	117 (67.63)	211 (42.71)	65 (33.68)	263 (55.49)	196 (60.68)	132 (38.37)	328 (49.18)
Caucasian, n (%)	56 (32.37)	283 (57.29)*	128 (66.32)	211 (44.51)*	127 (39.32)	212 (61.63)*	339 (50.82)
DM n (%)	35 (20.23)	96(19.43)	41(21.24)	90(18.99)	64(19.81)	67(19.48)	131(19.64)
Age (years)†	46.31 (11.41)	46.18 (13.05)	45.63 (13.06)	46.46 (12.47)	47.53 (11.84)	44.98 (13.24)*	46.21 (12.64)
Weight (lbs.)†	213.78 (55.75)	209.20 (58.09)	213.96 (66.56)	208.93 (53.36)	212.47 (54.73)	208.43 (59.97)	210.39 (57.49)
BMI†	33.73 (8.16)	33.10 (8.73)	33.80 (9.31)	33.04 (8.28)	33.35 (7.98)	33.19 (9.13)	33.26 (8.59)
Waist Cir(in.)†	42.11 (8.01)	41.35 (8.64)	41.74 (9.34)	41.46 (8.12)	41.87 (8.21)	41.23 (8.73)	41.54 (8.48)
Hip Cir†	45.45 (6.52)	45.50 (7.31)	45.89 (7.98)	45.32 (6.73)	45.55 (6.55)	45.42 (7.61)	45.49 (7.11)
WHR†	0.92 (0.10)	0.90 (0.10)*	0.90 (0.10)	0.91 (0.10)	0.91 (0.10)	0.90 (0.10)	0.91 (0.10)
Glucose(mg/dL)†	96.99 (39.34)	91.33 (36.01)	92.47 (37.32)	92.93 (36.84)	94.64 (39.79)	91.07 (34.06)	92.80 (36.95)
SBP(mm/Hg)†	126.91 (20.28)	125.31 (18.20)	123.22 (17.78)	126.76 (19.08)*	126.94 (18.93)	124.57 (18.56)	125.73 (18.77)
DBP(mm/Hg)†	80.60 (13.54)	77.62 (12.25)*	77.38 (13.03)	78.83 (12.49)	79.01 (12.36)	77.83 (12.93)	78.41 (12.66)
Total Cholesterol (mg/dL)†	186.76 (40.21)	183.56 (42.16)	180.88 (39.89)	185.82 (42.32)	187.41 (44.24)	181.53 (38.93)	184.38 (41.66)
Median Triglyceride (mg/dL) (IQR)	102.5 (83)	101 (77)	100 (82)	101 (80)	99 (79)	103 (82)	104.00 (46)
HDL-c(mg/dL)†	53.76 (16.51)	54.62 (16.18)	53.99 (16.73)	54.57 (16.07)	55.43 (16.72)	53.42 (15.77)	54.40 (16.26)
LDL-c(mg/dL)†	106.94 (32.36)	106.11 (33.71)	101.84 (30.83)	108.16 (34.19)*	108.63 (35.84)	30.71 (30.71)	106.32 (33.34)

+ = those with the polymorphims

− = those without the polymorphims

*P value <.05

†= data expressed as mean (standard deviation)

AA = African American

DM = diabetes mellitus

BMI = body mass index

Cir = circumference

SBP = systolic blood pressure

DBP = diastolic blood pressure

HDL-c = high density lipoprotein cholesterol

LDL-c = low density lipoprotein cholesterol

Table 2:

Adjusted OR for presence of CNR1 3813, CNR1 4895, and FAAH polymorphisms

OR (95% CI)	CNR1 3813	CNR1 4895	FAAH
Obese	1.22 (0.73, 2.02)	1.46 (0.91, 2.33)	1.17 (0.76,1.79)
Female	0.89 (0.55, 1.43)	0.79 (0.49, 1.26)	1.05 (0.69, 1.60)
AA	2.58 (1.73, 3.84) **	0.43 (0.29, 0.62) **	2.29 (1.63, 3.21)
Age	0.99 (0.98, 1.01)	1.003 (0.99, 1.02)	1.02 (1.003–1.03)
WHR	1.92 (0.13, 28.81)	0.17 (0.01, 2.37)	1.41 (0.13, 15.46)
SBP	------	0.99 (0.98, 1.004)	--
DBP	1.01 (0.997, 1.03)	----	0.996 (0.98, 1.01)
LDL-c	0.999 (0.99, 1.004)	0.99 (0.99, 1.000)	1.002 (0.997, 1.01)

* P<0.05

** p<0.001

AA = African American

WHR = waist hip ratio

SBP = systolic blood pressure

DBP = diastolic blood pressure

LDL-c = low density lipoprotein cholesterol