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RESEARCH ARTICLE

IS THERE AN ASSOCIATION BETWEEN 5-HT RECEPTOR (5-HT$_{2A}$) GENE PROMOTER POLYMORPHISM AND OBESITY?

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ABSTRACT

Introduction and objectives: Serotonin; (5-HT) is a neurotransmitter that has major role in energy homeostasis, behavior and mood changes; thus affects the individual's body weight and liability to obesity. 5-HT shows control over the appetite through different receptors with discrete functions. AA genotype of 5-HT$_{2A}$ gene promoter polymorphism was associated with increase receptor expression and binding. This study investigates the relation between the G1438A polymorphism of the 5-HT$_{2A}$ gene and the susceptibility to obesity.

Material and Methods: 189 individuals divided according to their BMI into control group with BMI < 25 Kg/m^2 and case group with BMI ≥ 25 Kg/m^2. The G1438A polymorphism of the 5-HT$_{2A}$ gene was detected by restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) of peripheral blood DNA samples.

Results: Genotype frequencies for AA and GA& GG were 25% and 75% respectively in the case group compared to 52.2% and 47.8% in the control group. Carriers of GA & GG genotype were at a significant high risk of developing obesity .Moreover; the mean energy intake per day was significantly increased among carriers of GA & GG genotype compared to AA genotype.

Conclusion: G allele is a risk factor for obesity.

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INTRODUCTION

Obesity which is state of high body mass index (BMI) ≥ 30 Kg/m^2 is considered a drastic worldwide health problem as it is associated with high incidence of type 2 diabetes, stroke, and coronary artery disease (Xavier, 2002 and Su Ying *et al*., 2009). The relative contributions of genetics and environment to the etiology of obesity have been evaluated in many studies. Although it varies from one study to another, yet about 30% - 40% of the variance in BMI can be attributed to genetics and 60% - 70% to environmental factors (Bjo¨rntorp, 1993). The role of genetics was illustrated by Bouchard *et al*., 1990 in a study of identical young-adult male twins who were overfed by 1000 kcal/d over a 100-day period.

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Among many candidate genes; 5-HT$_{2A}$ genes are of special interest given their role in appetite regulation. The human 5-HT$_{2A}$ gene is located on 13q14-q21, consists of three exons, and its genomic DNA spans over 20 kb (Su Ying *et al*., 2009). Serotonin (5-HT) is a neurotransmitter that is released in the synaptic junction and exerts its effect on specific receptors on the postsynaptic membrane. Serotonin receptors are a group of G protein-coupled receptors (GPCRs) and ligand-gated ion channels (LGICs) found in the central and peripheral nervous systems. They modulate the release of many neurotransmitters, including glutamate, GABA, dopamine, epinephrine/ norepinephrine, and acetylcholine, as well as many hormones, including oxytocin, prolactin, vasopressin, cortisol, corticotrophin, and substance P. Thus serotonin influences and regulates various biological and neurological processes such as aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, thermoregulation and hormone secretion

(Sargent and Henderson, 2011, Lam *et al*., 2010, Xavier, 2002, Dinan 1996). The involvement of 5- HT_{2A} gene in cortisol secretion suggests that genetic variation in 5- HT_{2A} receptor affects HPA activity and may be associated with the pathogenesis of abdominal obesity (Bjorntorp and Rosmond 2000, Rosmond *et al*., 2002, Dinan 1996). Moreover Serotonin reduces food intake and is probably involved in the etiology of anorexia nervosa and in weight regulation. Some studies have indicated a role for the 1438A/G variant in the pathogenesis of anorexia nervosa (Nishiguchi *et al*., 2001, Aubert *et al*., 2000, Nacmias *et al*., 1999, Campbell *et al*., 1998). This functional diversity stems from the ability of the neurotransmitter to interact with multiple 5-HT receptors that can trigger and activate distinct intracellular signaling systems. In this study we investigate the association between the 1438A/G promoter variant of the 5-HT_{2A} gene and the pathogenesis of obesity.

MATERIALS AND METHODS

It is a 15 month Case – control study of 189 females conducted in the internal medicine department and the central lab of Ain shams University hospital, Cairo, Egypt during the period of June 2008 - September 2009. The study was performed in accordance with the ethical standards laid down in the 1974 Declaration of Helsinki.

Subjects

Weight, height, waist and hip circumferences of all subjects were measured. Body mass index (BMI) and Waist hip ratio (WHR) were calculated. Subjects with body mass index (BMI) $\geq$ 25 kg/m^2 were considered positive for obesity as defined by World Health organization (WHO) (World Health Organization, 1998). Those with waist hip ratio (WHR) > 0.8 for women and > 0.9 for men were considered positive for abdominal obesity (World Health Organization, 1998). The study included 69 Females with BMI<25 Kg/m2 and mean age (36.1± 15.5) as control group and 120 females with BMI $\geq$ 25 Kg/m^2 and mean age (37.4± 14.7) as case group. The average calories intake per day for each subject was calculated from food sheet filled by the participating individuals for one month. All subjects received guidance from dietitian on the procedures for completing the dietary record and measuring food portion. Percent body fat was measured by using Citizen Body fat analyzer BM100 (Japan). A predesigned, validated questionnaire was filled to assure explaining the study purpose and procedures to participants, obtaining official consent and to facilitate data collection which included socio-demographic variables. Anonymity of the participants was maintained throughout the study.

Laboratory Tests

Lipids and lipid fraction measurements were performed using routine enzymatic tests (Diasys Kits) (Friedwald *et al*., 1997 and Rifal *et al*., 1999).

DNA Extraction

DNA was extracted from white blood cells by a salting-out method (Josef *et al*., 2002). Red blood cell lysis was done by using red cell lysis buffer (20 mM Tris-CL pH 7.6) followed by centrifugation. Nuclei lysis was carried by cell lysis buffer (10mM Tris-CL pH 8.0, 1mM EDTA pH 8.0, 0.1% (w/v) SDS) and protinase K (20 mg/ml) followed by centrifugation. Protein was precipitated by protein precipitation solution (60 ml of 5M potassium acetate, 11.5 ml of glacial acetic acid, 28.5 ml of water) followed by centrifugation. Finally DNA was precipitated by isopropanol and then ethanol 70% followed by centrifugation after each. Pellet of DNA was dried in air and rehydrated in TE buffer (pH 7.6) and stored in -20°C. The DNA purity and concentration were determined by spectrophotometer measurement of absorbance at 260 and 280 nm.

Polymorphism Detection

Gene was amplified by polymerase chain reaction on 96 well Amp PCR System 9700 Thermocycler (Applied Biosystems). Primer sequences, PCR conditions and restriction enzyme digestion were as follows (oligonucleotides were synthesized by Promega). The sequences of primers used for amplification of 5-HT_{2A} gene were 5'-AA GCTGCAAGGTAGCAACAGC-3'(forward) and 5'-ACCAACTTATTTCCTACCAC-3'(reverse). The thermal cycling procedure consisted of denaturation at 94°C for 30 seconds, annealing at 58°C for 30 seconds, and extension at 72°C for 30 seconds, repeated for 35 cycles, initial denaturation at 94°C for 5 min and final extension 72°C for 5 min. The PCR product was digested by Hpa II at 37°C. The 468-bp PCR product was cleaved into two fragments of 244 bp and 224 bp. Restriction products were resolved by electrophoresis on a 2.5% agarose gel stained with ethidium bromide (Figure 1).

Statistical Analysis

Genotype and allele frequency was calculated by allele counting (Emery 1986). Genotype distribution was investigated in relation to Hardy-Weinberg equilibrium. Three genotype groups will be considered for 5-HT_{2A} polymorphism (AA, GA, GG). Statistical analysis will be done with SPSS software version 11.0 (SPSS, Inc; Chicago IL). Difference in genotype prevalence and association between case and control group was assessed by the Chi-square, Correlation coefficient, Odds Ratio (OR) and 95% confidence interval (CI) was used to describe the strength of association. Mean serum levels for lipids, lipid fractions was compared between different allele groups using Student's t-test and Mann Whitney test for nonparametric data. P value <0.05 was considered significant.

RESULTS

This study had 189 female participant 69 in control group and 120 in case group with mean age of (36.1± 15.5) and (37.4± 14.7) respectively. The Genotype frequencies for AA and GA& GG in our study population were 25% and 75% respectively in the case group compared to 52.2% and 47.8% in the control group.

Table 1. Frequency and Odds Ratios of 5-HT $_{2A}$ Genotype among the studied groups in relation to BMI

Genotype	Control Group BMI<25kg/m^2 n=69	Case Group BMI≥25kg/m^2 n=120	OR	95% CI	X^2
AA	36(52.2%)	30 (25%)	3.3	1.7-6.1	14.2*
GA&GG	33(47.8%)	90(75%)			
Allele					
A	90(65.2%)	105(43.8%)	2.4	1.6-3.7	
G	48 (34.8%)	135(56.2%)			

*P <0.05

Table 2. Frequency and Odds Ratios of 5-HT $_{2A}$ Genotype in relation to waist hip ratio

Genotype	Normal WHR	Abnormal WHR	OR	95% CI	X^2
AA	45(52.2%)	21(25%)	2.6	1.4-4.8	8.9*
GA&GG	56(47.8%)	67(75%)			
Allele					
A	116(57.4%)	79(44.9%)	1.7	1.1-2.5	
G	86 (42.6%)	97(55.1%)			

*P <0.05

Table 3. Mean Level ± SD of energy intake and percent fat Among Carrier of Different Genotypes of 5-HT$_{2A}$

Parameter	AA (n=66)	GA&GG (n=123)
Energy intake(kcal/day)	1760±517.1	2109±440*
Percent Fat	26.5±4.7	29.4±5.7*

*P< 0.05

Table 4.Mean Level ± SD/mean rank of Different Parameters of lipid Profile among Carrier of Different Genotypes of 5-HT $_{2A}$ polymorphism**

Lipid Parameter	AA (n=51)	GA&GG (n=54)
TG (mg/dl)**	51.4	54.5
TC (mg/dl)	183.2±40.5	196.3±59.2
HDL (mg/dl)	38.7±10.8	39.4±13.2
DL (mg/dl	117.8±40.7	120.5±70.0

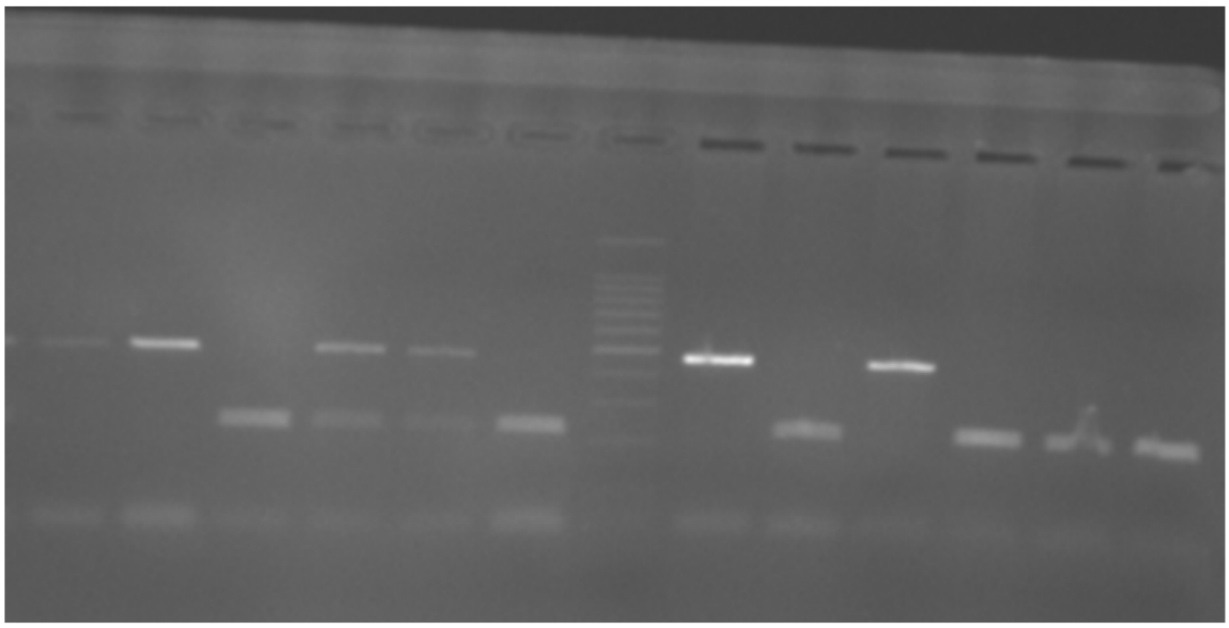

Figure 1. Agarose Gel electrophoresis for detection of 5-HT $_{2A}$ gene polymorphism after digestion with HpaII. Lane 1, 2, 8 and 10 AA(468 bp) genotype. Lane 3, 6, 9, 10, 11, and 12 GG (224 bp, 224 bp) genotype Lane 7 DNA marker. Lane 4, 5 GA genotype (468 bp, 224 bp, 224 bp)

Individuals with GA and GG genotype were more at risk to become overweight and obese (OR 3.3, 95% CI 1.7-6.1). Individuals with G allele were more at risk of becoming overweight or obese (OR 2.4, 95% CI 1.6-3.7) (Table 1). Table 2 shows that individuals with GA & GG genotypes were at higher risk of abnormal WHR (OR 2.6, 95% CI 1.4-4.8). Individuals of G Allele were more at higher risk of abnormal WHR. The mean Energy intake (expressed as Kcal/day) and the body fat percent were significantly higher in individuals with GA and GG genotypes compared to AA genotype (Table 3). There was no statistical significant difference in the lipid profile (Triglycerides, Cholesterol, LDL and HDL) between individuals with AA genotype and those with GA & GG genotypes (Table 4).

DISCUSSION

This study highlights the association between serotonin; 5-HT$_{2A}$ gene and obesity as we found significant differences in obesity between the different genotypes of 5-HT$_{2A}$genes and that AA genotype was more associated with lower BMI and normal WHR. This is in accordance with Bernard Herbeth *et al*., 2005 who found that A allele carriers had significantly lower intakes than did G allele carries without significant relation to maturation indexes as weight, height and body mass index.This is in consistence with Aubert *et al*., 2000 who found that the lower energy intake in overweight people carrying the A allele is concordant with higher frequency of this allele in anorexic patients. Some authors regard anorexia nervosa as a primary eating disorder, others consider it a possible alternative expression of mood disorder leading to decrease food intake. The serotonergic system is involved in both kinds of disorders. However, we cannot exclude the possibility that the association of the -1438A allele with low energy intake and fat intakes maybe due to linkage disequilibrium with other genetic polymorphism that could affect eating behavior, yet no candidate gene other than 5-HT$_{2A}$gene has been shown to be related to food intake in human.

This study showed that individuals with GA and GG genotype were at higher risk of high WHR and were more at risk to become overweight and obese. Individuals with G allele were at higher risk of high WHR more and at risk of becoming overweight or obese. This is in agreement with both Bernard Herbeth *et al*., 2005who found that – 1438G/A 5-HT$_{2A}$ polymorphism was associated with energy and fat intakes in young population and Rosmond, *et al*., 2002 who reported that homozygotes for the –1438G allele had increased body mass and abdominal distribution of body fat (WHR and abdominal sagittal diameter). Also a study on Japanese patients in 2001 found that the G allele of the 5HT$_{2A}$ receptor gene – 1438A/G polymorphism may be associated with eating disorders .These associations can be related to the alteration in the Hypothalamic-pituitary-axis (HPA). In addition, serotonin has a stimulatory role in the regulation of ACTH and cortisol secretion in man p16 through its binding to 5-HT$_{2A}$ receptor. A considerable amount of evidence has emerged regarding the pathogenic effect of cortisol in abdominal obesity. The involvement of 5- HT$_{2A}$ gene in cortisol secretion suggests that genetic variation in 5- HT$_{2A}$ receptor affects HPA activity and may be associated with the pathogenesis of abdominal obesity.

A common polymorphism of the 5-HT$_{2A}$ receptor gene (5-HT$_{2A}$) that has been identified is the 1438A/G gene in the promoter region. Studies have shown that variations in the 1438 SNP modulates 5-HTR$_{2A}$ promoter activity, with the AA genotype associated with higher 5-HT$_{2A}$ gene expression in cell lines that endogenously express 5-HT$_{2A}$ (Parsons *et al*., 2004). Aubert *et al.,* 2000 suggested that 1438A>G promoter polymorphism may influence food and alcohol intake in obese subjects. On the other hand in 2009 Su Ying *et al*., suggested that genetic polymorphism 1438A>G of the 5-HT$_{2A}$was not significantly associated with obesity, but G allele tends to increase abdominal adipose tissue depot in obese men. The explanation of the association of genotype GG with abdominal fat deposit in men with obesity is ambiguous, in one hand the minor genes of obesity as the 5-HT $_{2A}$ gene would have a relatively small effect on the development of obesity and it would require time and the occurrence of other genetic and environmental factors for complete development. Accordingly Rosmond *et al*., 2002 state that the genotype GG is associated with being overweight and abdominal fat deposit (defined by waist circumference), but not with obesity. On the other hand, it seems that there is differential expression of the components of 5-HT $_{2A}$ in adipose tissue depending on the location.

Thus this expression would be greater in omental tissue. Other studies suggest that the 5-HT$_{2A}$ 1438A>G promoter polymorphism may influence food and alcohol intake in obese men. It is important to mention that the – 1438G/A polymorphism could be also associated with personality or behavior traits that were related to food intakes and that several studies hypothesized that persons carrying the – 1438G/A have altered mood or other personality characteristics that would be associated with food intake (Ham BJ *et al*., 2004, Kaye *et al*., 2004 and Sher L. 2001). We also found that the mean energy intake (expressed as Kcal/day) and the body fat percent were significantly higher in individuals with GA and GG genotypes compared to AA genotype. This in coherence with Pérusse *et al*., 1988, who found significant genetic influences on macronutrient intakes (11% for protein and 20% for fat and carbohydrate) but not on total energy intake and with Aubert *et al*., 2000 who found that A allele was significantly associated with lower energy intake and associations with total, monosaturated and saturated fats were of borderline significance. 1438A allele is significantly associated, according to a meta-analysis of case- control studies, with anorexia nervosa.

Mitchell *et al*., 2003 in the San Antonio Family Heart Study reported that the familial relations accounted for 13–26% of the total population variation in total energy, fat, and carbohydrate intakes and the study reported linkage between body mass index and the D13S257 genetic marker located in the same chromosomal region (13q14) as the 5-HT$_{2A}$ gene. In addition in that study, familial influences were stronger when modeled as a genetic heritability than as a shared household effect. Moreover, results of a study of twins reared apart revealed higher correlations among monozygotic than dizygotic twins which suggest that 20-30% of the variance in total energy and macronutrient intake could be determined by genes (Hur Y M *et al*.,1998). In this study there was no statistical significant difference in the lipid profile between

individuals with AA genotype and those with GA & GG genotypes, which is similar to Rosmond, 2002 who did not find a significant difference in lipid profile across the -1438G/A genotype groups. The role of serotonin (5-HT_{2A}) in regulating food intake was shown in animal models, where specific agonists of 5-HT_{2A} decreased the neuropetide Y-stimulated food intake (Currie and Coscina, 1998) and the 5-HT induced hyperphagia was antagonized by 5-HT_{2A} receptor antagonists (Sugimoto *et al*., 2002). There is evidence that some selective serotonin reuptake inhibitors are effective as anti-obesity drugs such as fluoxetine, it produce a resumption of the normal eating pattern by diminishing meal size and disrupting night-eating behavior. The limitation of this study could be: the small sample size thus cannot confirm and generalize the finding; the dietary data of the participants were self- reported thus the food intake assessment could be less reliable and the participants were all Egyptian females thus no sex / genotype interactions were studied and effect ethnicity was not assessed and evaluated.

In conclusion, in spite of the limitations of the study, these data show that a gene polymorphism of the serotonergic system could be related to obesity and eating behavior in humans. We recommend, independent, confirmatory studies, large samples studies that involve different gender, ethnicity and age groups for definite conclusions about the role of this polymorphism in the physiology of the eating behavior and the pathogenesis of obesity.

Conflict of Interest: None. The authors declare that they have no competing interests.

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