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Research Report

Polymorphism in the PPARgamma2 and beta2-adrenergic genes and diet lipid effects on body composition, energy expenditure and eating behavior of obese women ☆

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Abstract

In order to evaluate the effect of polymorphism in the PPARgamma2 and beta2-adrenergic genes and diet lipids on body composition, energy expenditure and eating behavior of obese women, 60 subjects were submitted to anthropometric, biochemical, dietary, molecular, basal and postprandial metabolism (indirect calorimetry) and eating behavior (visual analog scale) evaluation. Fat and saturated fatty acid (SFA) high diet was used to assess postprandial metabolism. The frequency of Pro12Pro/Gln27Gln, Pro12Pro/Gln27Glu, Pro12Pro/Glu27Glu and Pro12Ala/Gln27Glu genotypes was 35.71%, 30.37%, 23.21% and 10.71%, respectively. These values were not significant ($p > 0.05$) for the dietary, anthropometric, biochemical and metabolic parameters. The Pro12Ala/Gln27Glu group was found to present greater energy used in postprandial period (EUPP). The presence of the PPARgamma2 gene variant, independent of beta2-adrenergic gene polymorphism, resulted in fat oxidation increase. Also, this group presented higher satiety, compared to the Pro12Pro/Gln27Gln group. The presence of the variant alleles in the PPARgamma2 gene suggests benefits in food intake control.

Keywords: Obesity; PPARgamma2; Beta2-adrenergic receptor; Diet; Energy metabolism; Eating behavior

Introduction

The prevalence of overweight and obese people is increasing worldwide in both developed and developing countries (Document of Latin American Consensus on Obesity, 1999). In Brazil, overweight rates for the population over 20 is 40.6%, with obesity rates of 8.8% for men and 12.7% for women (POF, 2004). In Spain, 11.9% men and 13.6% women are obese (Martínez, Moreno, & Martínez-Gonzales, 2004).

Low-energy expenditure and increase in food intake are involved in obesity, with the most important factors being difficult to determine (Bray, 1976; Monteiro & Halpern, 2000; Wolff, 1997).

The risk of developing obesity has a genetic component and many studies have quantified *loci* and candidate genes involved in its etiology. Human genome sequencing has offered numerous benefits to the study of genetic polymorphism, helping identify possible risks caused by the alleles, in addition to the development of genomic technologies that favor the study of diagnosis and treatment of obesity (Kowalski, 2004).

According to Perusse et al. (2001), this number is increasing, with a total of 54 new *loci* being added to the genetic map of human obesity last year, and the number of

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marked genes and chromosomal regions that have been associated with human obesity being presently around 250. Additionally, an increase in DNA sequence alterations in genes specific to the obesity phenotype has become evident, with 130 studies reporting positive association with 48 candidate genes. The genetic map of obesity reveals that the *loci* affecting obesity-related phenotypes may be found in all chromosomes, except Y.

Efforts to identify candidate genes for obesity have concentrated on adipose tissue, since thermogenesis regulation through the symphatic nervous system carried out by the brown adipose tissue is mediated by the beta-adrenergic receptors. Also, the PPARgamma (peroxisome proliferators-activated receptor gamma) plays an important role in adipogenesis and may control 30 genes responsible for the environmental signs linked to nutrients, such as fatty acids (Froguel & Boutin, 2001).

The PPARgamma2 gene is expressed preferably in differentiated adipocytes (Medina, Sewter, & Vidal-Puig, 2000) and mediates the expression of specific fat tissue cell genes (Spiegelman, Castillo, Hauser, & Puigservar, 1999) that codify proteins directly related to the lipogenic pathways (Desvergne & Wahli, 1999). Hence, this gene affects the fatty acid stock in fat tissue, participating in adipocyte differentiation by inducing pre-adipocyte maturation in fat cells. It acts by stimulating hydrolysis of the circulating triglycerides (TG) and subsequent entry of the fatty acids in the adipose cells. It also stimulates binding and activation of cytosol fatty acids, events required for TG synthesis (Gregoire, Smas, & Sul, 1998; Kersten, Desvergne, & Wahli, 2000) and participates also in adipocyte hypertrophy (Kubota et al., 1999).

Fat tissue accumulation occurs by means of three mechanisms: proliferation of pre-adipocytes found in fat deposits, its differentiation in adipocytes capable of storing fat, and through imbalance between lipogenesis and lipolysis, favoring the former. All these events are dependent on environmental and genetic factors. Adipogenesis persists throughout life and may be influenced by diet size, frequency and composition. Certain adipogenic transcription factors, such as PPARgamma, which interacts with cell-cycle regulating proteins, once modified, result in changes in gene expression related to adipogenesis (Palou, Bonet, & Rodríguez, 2001).

Malczewska-Malec et al. (2004) evaluated the relation among risk factors associated with obesity, including insulin-resistance, lipid tolerance, arterial hypertension, endothelial function and genetic polymorphisms; with appetite regulation, adipocyte differentiation and insulin-sensitivity, thermogenesis and fatty acid catabolism. The relation between obesity and certain genetic polymorphisms was observed.

Polymorphism of the PPARgamma2 gene is characterized by proline-to-alanine substitution at codon 12 (Deeb et al., 1998).

Studies on obese men and women show conflicting results when considering the relation between the variant in PPARgamma2 gene and obesity (Bearmer et al., 1998; Valve et al., 1999). Deeb et al. (1998) suggest that polymorphism of the PPARgamma2 gene has been associated with reduction of body mass index (BMI) (Deeb et al., 1998) and alteration of gene function. Kubota et al. (1999) evaluated mice with one function allele in the PPARgamma gene (Pro12Ala), and verified resistance to obesity development. However, Valve et al. (1999) observed that obese women with the Ala12Ala genotype had increased BMI, lean body mass, fat mass, and waist and hip circumferences compared with the women with the Pro12Pro or Pro12Ala genotypes.

There are various ligands of this gene (Houseknecht, Cole, & Steele, 2002; Mori et al., 1998), including polyunsaturated fatty acids (PUFA) (Azcárate, Moral, & Hernández, 2000; Houseknecht et al., 2002). Thus, change in the PUFA content in the dietary content could increase lipogenesis in subjects without the variant allele in the PPARgamma2 gene.

Dietary fatty acids influence various metabolic routes in an array of organs. Part of this influence causes alteration in mRNA activation. Under intense energetic restriction or fasting, activation of TG removal from the fat tissue occurs and large amounts of fatty acids are released into the liver, with the events occurring in this organ being influenced by PPAR (Kersten et al., 2000). On the other hand, high-fat diets promote adipocyte differentiation (Margareto, Larrarte, Marti, & Martínez, 2001; Vidal-Puig et al., 1996). Low fatty acid levels in animals fed high fat diets may occur because such diets could induce fat accumulation, using the circulating fatty acids (Berraondo, Marti, Duncan, & Martínez, 2000). With a high-fat diet adipocyte increased hypertrophy and insulin resistance are produced, while in rodents with polymorphism of the PPARgamma gene, the same effect has not been observed (Kubota et al., 1999).

In contrast, the beta2-adrenergic receptors are mediators of the lipolytic effects of the catecholamines (Meirhaeghe et al., 2001), participating in energetic homeostasis, since they stimulate the reduction of glycogen use and the increase of lipid mobilization (Arner, 2001). The beta2-adrenergic receptors (β2-AR) gene was found to be expressed in subcutaneous fat tissue (Large et al., 1997). However, abdominal fat has a higher density and sensitivity to the beta-adrenergic receptor gene, and in obese individuals with increase waist circumference (WC), beta2-adrenergic gene activity is higher (Meirhaeghe et al., 2001). The presence of the variant in this gene, characterized by a glutamine-to-glutamic acid substitution at codon 27, is associated with body weight gain (Hellström, Large, Reynisdottir, Wahrenberg, & Arner, 1999).

Thus, when considering the functions of the evaluated genes, it is suggested that polymorphism of the beta2-adrenergic receptor gene promotes body weight gain in subjects on high fat diets, since it could reduce oxidation of the ingested fat. On the other hand, polymorphism of the PPARgamma2 gene would facilitate body weight loss in the presence of a high fat diet.