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Obesity, Leptin and Leptin Receptors

Saeed Khosropour,[1] Maryam Shojaee,[2,*] and Peyman Lotfi[3]

[1]Department of Medical Biochemistry, Hamedan University of Medical Sciences, Hamedan, IR Iran
[2]Department of Biology, Payam Noor University of Mashhad, Mashhad, IR Iran
[3]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, IR Iran

[*]*Corresponding author*: Maryam Shojaee, Department of Biology, Payam Noor University of Mashhad, Mashhad, IR Iran. E-mail: m.shojaee2407@gmail.com

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Obesity is one of the primary challenging health issues of the current century. The prevalence of obesity in Iran is increasing. Childhood obesity boosts the risk of adult obesity, which is really threatening the next generations (1). It is considered as one of the most important risk factors for type 2 diabetes, hypercholesterolemia, hypertension and cardiovascular diseases. The etiology of human obesity has a complex pathogenesis due to the interactions between genetic factors, environmental factors and life style. The former brings about 40% - 70% of the obese phenotype. Up to now, the causes of this lethal epidemic are not evidently established. However, high calorie intake along with the sedentary modern lifestyle is the main provider of this state. Furthermore, scholars believe that genetic factors impose a key role in the etiology of obesity as well (2). Currently, complex gene-environment interactions are responsible for the present epidemic issue. Genetic variations, specifically single nucleotide polymorphisms (SNPs), can contribute to individual's susceptibility to particular metabolic disorder, but not as the single disease-triggering factors (3). Among 118 genes nominated and associated with obesity, the leptin and leptin receptor genes were of major interest by scholars. These genes are examined for gene polymorphisms and are potentially linked to the pathophysiology of obesity (4). Mutations in leptin and leptin receptor genes give rise to severe early-onset obesity with a fast and impressive increase in weight soon after birth. In 1994, leptin was identified as the "obese (ob)" gene product. Leptin is chiefly produced in adipose tissue (5, 6). It attracted much attention as a critical factor in the regulation of energy homeostasis, insulin sensitivity, and lipid and carbohydrate metabolism.

Leptin, a metabolic and neuroendocrine hormone, regulates body mass control, energy expenditure and neuroendocrine function. Its level extremely depends on the presence of fat in the cells. It is mainly secreted by adipocytes and circulates in lean individuals at the level of 5 - 15 ng/mL. The deficiency of leptin leads to augmented appetite and food intake that give rise to morbid obesity (7).

Leptin exerts its physiological activity directly through a membrane receptor, and a single transmembrane protein of cytokine receptor superfamily located in various tissues, including the brain (8). Among all six spliced leptin receptor, the long isoform is of specific physiologic significance due to its weight-reducing effects.

Several polymorphisms of both leptin and leptin receptor genes were studied in diverse populations for its probable relationship with obesity and the related complications.

The Q223R polymorphism in leptin receptor is linked with body mass index (BMI), fat accumulation, leptin concentration and blood pressure. Furthermore, a number of common polymorphisms and rare polymorphisms of the long isoform of leptin receptor gene are studied and evaluated in various populations. Some studies found considerable correlation between obesity and polymorphisms of the leptin receptor gene (9, 10); however, some others did not succeed to uncover major associations (9). It is obvious that these indecisive outcomes might be the result of differences in populations and fairly restricted number of study populations (10). Moreover, a leptin gene SNP substitution G to A at nucleotide 2548 upstream of the ATG start codon in the gene promoter is associated with obesity amplified leptin production and secretion.

Despite the controversial reports and developments, it seems that there is still a need for further investigations in this field to obtain more definitive results.

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