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MOLECULAR BASIS OF THE DEVELOPMENT OF INSULIN RESISTANCE IN OBESE ADOLESCENT AND ADULT MEN

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Obesity is a serious and urgent public health problem because the number of people including children with severe obesity is significantly increased. Furthermore, children with severe obesity are at greater risk for adult obesity, early atherosclerosis, hypertension, metabolic syndrome, type 2 diabetes, fatty liver disease, and premature death. The development of obesity and its metabolic complications is associated with dysregulation of various intrinsic mechanisms, which control basic metabolic processes, including cellular growth, glucose, and lipid metabolism as well as insulin sensitivity, via changes in the expression of numerous regulatory genes including genes related to glucose metabolism and their regulations [1-3]. Moreover, obesity and its complications result from interactions between genes and environmental factors and is associated with changes in gene expressions of regulatory network in various organs and tissues, but preferentially in adipose tissue. Therefore, adipose tissue growth is in a center of obesity and is tightly associated with the glucose and lipid metabolism as well as with cell proliferation processes and is controlled by different interconnected regulatory factors and enzymes. At the same time, the blood reflects numerous changes in different organs and tissues in diseases including obesity. Special interest deserves the key regulatory enzymes and factors, which control glucose and lipid metabolism as well as cell growth. Receptors of insulin-like growth factor (IGF) and insulin as well as related proteins play an important role in the regulation of numerous metabolic and proliferative processes and participate in endoplasmic reticulum stress, which is an important factor of obesity, insulin resistance, and tumor growth. Furthermore, there exists a cross talk between IGF and insulin receptor signaling pathways at the receptor level or downstream signaling level. A specific feature of obesity and associated insulin resistance, as well as a number of other pathological conditions, is impaired maturation of proteins in the endoplasmic reticulum and the accumulation of unfolded or improperly folded proteins, called endoplasmic reticulum stress. This stress is an important factor in the development of insulin resistance, as well as many metabolic complications in obesity, because the endoplasmic reticulum stress disrupts the signaling pathways from the insulin receptor. Therefore, endoplasmic reticulum stress is a factor that controls the expression of a large number of genes, including those that control glucose metabolism, and links obesity and its complications.

The aim of this work was to study the association between the expression of glucose metabolism related genes and insulin resistance, which expression is changed in obese adolescents and adult men with and without insulin resistance, for better understanding the molecular basis of the development of obesity complications and evaluation of possible contribution of these genes in development of insulin resistance.

Methods. The expression level of genes related to glucose metabolism and their regulations was studied by real-time qPCR in adipose tissue and blood cells using SYBRGreen Mix and specific for each mRNA forward and reverse primers. Total RNA was extracted using TRIZOL reagent. For reverse transcription of mRNAs we used Thermo Scientific Verso cDNA Synthesis Kit (Germany). The values of mRNA expressions were normalized to the level of ACTB mRNA and represented as percent of control (100%).

Results. It was shown that in obese patients with insulin resistance the expression level of IRS1 (insulin receptor substrate 1), *HK2* (hexokinase 2), *PFKFB2* (6-phosphofructokinase/fructose-2,6-bisphosphatase 2) and *PFKFB3* as well as circadian factors *CLOCK* and *ARNTL* genes in subcutaneous adipose tissue is significantly decreased as compared to obese men with normal sensitivity to insulin. At the same time, the development of insulin resistance in obese patients leads to up-regulation of *PFKFB4, PER1, HSPA6, ALDH1A3, COL5A1, TIMP1, TIMP2, SPARC*, and *VCAN* gene expressions in subcutaneous adipose tissue. The expression level of IGF1 (insulin-like growth factor 1) and *IGFBP5* (IGF binding protein 5) as well as *ENO1* (enolase 1) and *ENO2* is down-regulated in the blood of obese adolescent with insulin resistance, but *IGFBP2* and *IGFBP7* gene expressions are significantly increased in these patients.

Discussion. It is possible that the changes in the expression of *IRS1, IGF1, IGFBP2, IGFBP5*, and many other regulatory genes are mediated by the endoplasmic reticulum stress and contribute to the development of insulin resistance and glucose intolerance as well as to other complications [3].

Conclusions. The results of this investigation provide evidence that the development of insulin resistance in obese patients is associated with gene specific changes in the expression of many very important regulatory genes, which are endoplasmic reticulum stress responsible.

Key words: obesity; insulin resistance; genes; subcutaneous adipose tissue.

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