Streszczenie w języku angielskim

The receptor for advanced glycation end products as a common point of metabolic pathways for obesity and its complications

Obesity is a chronic disease characterized by the excessive accumulation and abnormal functioning of adipose tissue. This results in several adverse health consequences. Currently, it is one of the key health challenges, as it is a risk factor for approximately 200 complications, including metabolic and cardiovascular diseases. These complications result in an average reduction in life expectancy of 6 years for men and 7 years for women. The basic pathogenic mechanism linking excessive body weight to organ complications is chronic inflammation caused by dysfunctional adipose tissue (metabolic inflammation). Previous studies based on animal models have shown the significant contribution of the receptor for advanced glycation end products (RAGE) pathway to obesity-related metabolic inflammation.

This doctoral dissertation consists of three published papers that aim to describe the role of the RAGE pathway in the development of obesity-related cardiometabolic complications in humans. The series includes one review paper and two original papers.

The first paper, titled "Receptor for Advanced Glycation End Products (RAGE) Pathway in Adipose Tissue Metabolism", summarizes the current knowledge about the role of the RAGE signaling pathway in adipose tissue dysfunction in obesity and related metabolic complications. The introduction describes adipose tissue as an endocrine organ and highlights the mechanisms that lead to its dysfunction in obesity. It is then followed by a description of the role of advanced glycation end products (AGEs) and the RAGE pathway in regulating adipose tissue activity. Additionally, the dissertation describes current research on the RAGE pathway in animal models and humans, analyzing the pathway's importance in the development of obesity and its accompanying complications. Finally, we present therapeutic perspectives aimed at reducing the AGE pool and inhibiting the RAGE pathway as a potential strategy for treating obesity and its complications.

The second paper, titled "AGER-1 Long Non-Coding RNA Levels Correlate with the Expression of the Advanced Glycation End-Product Receptor, a Regulator of the Inflammatory Response in Visceral Adipose Tissue of Women with Obesity and Type 2 Diabetes Mellitus," analyzes the expression of the advanced glycation end-product receptor gene (*AGER*) and long non-coding RNA AGER-1 (lncAGER-1) in adipose tissue in the context of obesity and type 2

diabetes, examining their correlation with inflammation severity. The study revealed that obesity is associated with increased *AGER* mRNA expression in subcutaneous adipose tissue, which decreases with weight loss. The same trend was observed for lncAGER-1, whose level additionally correlated with *AGER* expression in the adipose tissue of women with obesity and type 2 diabetes. Furthermore, a positive correlation was found in this group between *AGER* mRNA levels and the expression of genes encoding inflammatory mediators.

The third paper, titled "Advanced Glycation End-Product Receptor Gene (RAGE) Polymorphism in Patients with Acute Coronary Syndrome: A Case-Control Study in the Polish Population," focuses on the impact of two single nucleotide polymorphisms (SNPs) in the RAGE-encoding gene – *AGER* (rs2070600 G/A and rs184003 G/T) on predisposition to acute coronary syndrome and ischemic heart disease in the Polish population. The study observed a higher frequency of genotypes containing the T allele (GT + TT) of the rs184003 polymorphism in patients with acute coronary syndrome. Additionally, carriers of the rs184003 T allele were characterized by significantly lower high-density lipoprotein (HDL) cholesterol levels and higher troponin I levels at the time of acute coronary syndrome onset. No significant association was found between the rs2070600 polymorphism and the risk of acute coronary syndrome. Notably, no significant correlations were observed between the studied polymorphisms and the degree of coronary artery stenosis as assessed by angiography.

In summary, the results suggest a potential role for lncAGER-1 in regulating the expression of the RAGE gene (*AGER*) in adipose tissue of obese patients, as well as a link between increased *AGER* expression, metabolic inflammation, and the risk of developing type 2 diabetes. Furthermore, this study demonstrated that the presence of the T allele of the rs184003 *AGER* polymorphism may predispose individuals in the Polish population to the development of coronary artery atherosclerosis and its complication, acute coronary syndrome. However, the rs184003 G/T and rs2070600 G/A *AGER* polymorphisms were not associated with the occurrence of acute coronary syndrome at a young age (before 50 years old) in the analyzed population.