11. Streszczenie w języku angielskim

Hypertension is one of the most common cardiovascular diseases. It is estimated that half of the human population suffer from this disorder. Chronic pressure overload negatively affects, in particular, the heart muscle causing its hypertrophy. Under physiological conditions, ATP generated in the heart muscle comes mainly from long-chain fatty acids (LCFA; 60-70%) and to a lesser extent from glucose (20-30%). Recent studies indicate that hypertension induces a shift in myocardial energy substrate preference toward glucose with concomitant reduction of LCFA oxidation. Additionally, it has been shown that the degree of LCFA oxidation impairment correlates with the advancement of left ventricular hypertrophy and may be responsible for the reduction of myocardial capacity in hypertension.

The properties of cannabis were known in ancient times. It was used, among others, in the treatment of insomnia, convulsions, depression, and also served as an anesthetic and analgesic as well as appetite stimulant. The discovery of delta-9-tetrahydrocannabinol (THC) in 1964, as a substance responsible for the pharmacological effects of marijuana, increased interest in the possibility of cannabinoids introduction for the therapy of various diseases. Experiments carried out in this area demonstrated the existence of the endogenous cannabinoid system (ECS). Its structure is similar to other body signaling systems, and includes ligands such as anandamide (AEA), cannabinoid receptor type I and II, which belongs to the family of 7-transmembrane receptors, and enzymes involved in the synthesis, uptake, and degradation of endocannabinoids. Although ECS does not exert significant involvement in the regulation of the cardiovascular system under physiological conditions, it plays an important role in pathological states. Studies have shown that plasma level of AEA was elevated in hypertensive patients as well as rats, indicating ECS participation in this disease. Interestingly, inhibition of the enzyme responsible for the degradation of AEA, fatty acid amide hydrolase (FAAH), reduces blood pressure in hypertensive rats to normotensive levels. Numerous reports describe the role of endocannabinoids in the regulation of energy metabolism. However, it is still unknown how ECS affects heart metabolism. Therefore, the purpose of current study was to determine the role of endocannabinoids in cardiac metabolism under hypertensive conditions.

In the present study, we have shown that hypertension reduced fatty acid oxidation (palmitic acid oxidation: -40.5% vs control group) and simultaneously increased

glycolytic metabolism (intramyocardial glycogen content: -44.1%, pyruvate dehydrogenase - PDH expression: +30.1% vs control group) in the left ventricle. We observed that palmitic acid oxidation in the hypertensive rats after chronic ECS activation was decreased to the same extent as in the hypertensive group alone (-40.2% vs the normotensive group). Additionally, chronic FAAH inhibition in hypertensive rats caused changes in total (FAT/CD36: -18.7%, FATP1: +14.4% vs control group) and plasmalemmal (FAT/CD36: +26.3%, FATP1: -12.8% vs control group) expression of fatty acid transporters in the left ventricle. However, there was unchanged myocardial fatty acid uptake (uptake of radioactively labeled palmitate: $P > 0.05$ vs control group). Nevertheless, chronic ECS activation in hypertensive rats increased the intramyocardial accumulation of triacylglycerols (TAG: +21.9% vs control group), presumably by reducing the rate of TAG hydrolysis to the diacylglycerol fraction (DAG: -20.2%, adipocyte triacylglycerol lipase - ATGL expression: -19.6% vs control group). Interestingly, chronic URB597 administration in hypertensive rats led to an increased plasmalemmal expression of major glucose transporters (GLUT1: +29.2%, GLUT4: +28.5% vs control) and subsequent restoration of the intramyocardial glycogen pool (+47.3% vs hypertensive group). Despite this compensation, we found that intensification of glycolysis was the same as in hypertensive group alone (PDH expression: +31.1% vs control group). In parallel, an increase in the expression of the enzyme catalyzing the first step of the Krebs cycle, citrate synthase (+21.2% vs the control group) was observed. This indicates that chronic FAAH inhibition may support mitochondrial energy generation in the hypertensive heart.

The results of this investigation prove that chronic activation of ECS under hypertensive conditions positively affects glucose but not LCFA metabolism in the left ventricle.