Abstract

Obesity and associated metabolic disorders, called as “metabolic syndrome”, currently represent a major social and economical problem of public health. From the energy balance point of view, long-lasting energy surplus leads eventually to massive accumulation of energy stores resulting in various adverse effects on metabolism and health. General goal of the thesis was to examine these metabolic disorders at cellular and whole-body level using suitable mouse models. The main focus was on the most metabolically active tissue, namely skeletal muscle, liver and adipose tissue and on the regulatory roles of AMP-activated protein kinase (AMPK) and leptin in the energy metabolism.

The whole thesis is based on four published studies. Two studies were focused on skeletal muscle. In the first study, we proved the involvement of leptin and AMPK in the metabolic response to high-fat diet-feeding. We described a mechanism of muscle non-shivering thermogenesis based on enhanced lipid catabolism, which contributes to the genetically-determined resistance of inbred A/J mice to obesity. Such mechanism was not operating in obesity-prone C57BL/6 mice. In the second study, performed using C57BL/6 mice, we have described beneficial effect of combination treatment using n-3 polyunsaturated fatty acids (n-3 PUFA) of marine origin and anti-diabetic drug rosiglitazone, We have found that synergistic induction of muscle insulin sensitivity by the two interventions was responsible for marked beneficial effects of the combination treatment on both whole-body glucose homeostasis and metabolic flexibility. The third study was focused on the liver and the involvement of AMPK in beneficial treatment by the marine lipids. Using C57BL/6 mice with genetic disruption of one of the catalytic subunits of AMPK (AMPKα2 knock-out mice), we have revealed that AMPK is required for preservation of hepatic insulin sensitivity by n-3 PUFA in the context of high-fat-feeding. In the last study, conducted using C57BL/6 mice, 5′-iodothyronine deiodinase (deiodinase 1) activity in adipose tissue was found to be stimulated by leptin, and, therefore, a novel regulatory mechanism controlling lipid metabolism in adipose tissue and possibly also accumulation of the tissue was described.

In conclusion, this thesis provides new findings in the field of obesity and regulation of energy metabolism, and it also supports the importance and power of using specific mouse strains in the field of experimental obesitology, as well as the requirement of proper choice of the right strain for studying specific topics and hypothesis.