Abstract

Obesity is a frequent metabolic disease that causes many other health and socioeconomic complications. Obesity arises due to excessive energy intake and decrease in energy expenditure, which is a conseqence of contemporary lifestyle. Moreover, obesity has a strong genetic component. Common obesity is polygenic, multifactorial disease, in which individual genes interact with each other and with environmental factors. Genome-wide association studies, conducted between 2006-09, led to the discovery of dozens of gene loci that predispose individuals to obesity. The strongest signals were registered for polymorphisms in *FTO* (*fat mass and obesity-associated*) and near a gene *MC4R* (*melanocortin 4 receptor*). However, the contributions of these variations on the phenotype of obesity are very small, therefore, it is necessary to validate the results of such robust studies. It is very important to uncover the effects of genetic variants for understanding the molecular mechanisms of energy metabolism.

The studies presented in this thesis refer about the impact of polymorphisms in selected genes on anthropometric and metabolic parameters of the patients of the Institute of Endocrinology and of healthy volunteers who underwent functional tests. Our cohort includes a representative sample of Czech children (COPAT study). DNA samples were genotyped for the selected single nucleotide polymorphisms. In the group of normoglycaemic women, a significant association of *MC4R* gene with the higher level of growth hormone and leptin and better glucose homeostasis was found. This suggested a complex role of MC4R in the hypothalamic regulation. The effect of the *FTO* gene variation in lean women was also investigated. In this group, a haplotype combination of four risk variants was associated with BMI. A likely explanation for their lean phenotype could be the finding of higher levels of growth hormone. The usage of oral contraceptives has deepened the metabolic effect of the risk haplotype. We searched the associations of selected genes also in the cohort of adolescents, as the metabolic diseases are increasingly emerging by adolescents too. We found a correlation of polymorphisms in genes *MC4R* and *BDNF* with metabolic syndrome. Association of polymorphism in the *FTO* gene overweight and obesity has been confirmed. A gene variant in *TMEM18* was associated with underweight and variant in *PCSK1* was associated with lower glucose levels, esp. in boys.

The next part of this thesis focuses on effects of bariatric operations, which are currently considered the most effective tool in the treatment of obesity. Their effect is not only weight reduction, but also the treatment of other diseases associated with obesity

(type 2 diabetes, dyslipidaemia, hypertension). Mechanisms that improve metabolic profile in just a few days after surgery have been studied intensively. In our studies, we investigated the effect of three types of bariatric surgery – laparoscopic gastric plication (LGP), laparoscopic gastric banding (LAGB) and biliopancreatic diversion (BPD). Reduced weight and improved glucose metabolism occurred after all three operations, but only BPD led to the complete remission of type 2 diabetes. After LGP, incretin levels have changed. This was apparently responsible for short-term improvement in glucose metabolism. However, two years after LGP blood glucose levels have increased to the baseline levels. In women after BPD, we found increased lipogenesis in adipose tissue, indicating an adaptation of the organism to degraded resorption of fatty acids from food. This type of surgery has led to the most satisfying overall metabolic status of patients.