SUMMARY
It is well established that n-3 polyunsaturated fatty acids with long chain (n-3 LC-PUFA) have beneficial effects on the obesity-induced metabolic disorders in mice. However, in obese humans, the potency of these fatty acids to positively affect obesity and insulin resistance has been shown to be lower. The aim of the studies described in this thesis was to verify various approaches aimed at increasing efficiency of n-3 LC-PUFA and to study the involvement of 2 subunit of AMP-activated protein kinase (2-AMPK) in the mechanisms of action of these compounds.
Firstly, various chemical derivatives of DHA were tested in mice. Substance-2, the -ethyl ester of DHA, completely prevented and even partially reversed the development of obesity, fat accumulation, impaired glucose tolerance, dyslipidemia and white adipose tissue inflammation, even though the dose was only 10 % of that normally used in mice for the treatment with n-3 LC-PUFA. Secondly, the combination of n-3 LC-PUFA and a low-dose of anti-diabetic rosiglitazone prevented, in additive manner, development of dyslipidemia and insulin resistance, reduced the accumulation of body fat and adipocyte hypertrophy, while inducing adiponectin in mice fed a high-fat diet. This treatment also reversed impaired glucose tolerance in obese mice.
The major part of this thesis was aimed to study the mechanism of n-3 LC-PUFA action and the possible involvement of 2-AMPK. We found, by using the model of 2-AMPK knockout mice, that beneficial effects of n-3 LC-PUFA on the prevention of insulin resistance were mediated by 2-AMPK. The liver appeared to be the site of a dominant effect of n-3 LC-PUFA, since their inclusion in the diet resulted in the activation of 2-AMPK primarily in the liver and improved hepatic insulin sensitivity in the 2-AMPK-dependent manner. The improvement of liver insulin sensitivity was not associated with the changes in liver triacylglycerol levels; however, it was closely related to the content of diacylglycerols that are known to affect insulin sensitivity. Similarly to hepatic insulin sensitivity, also the effect of n-3 LC-PUFA on diacylglycerol levels was 2-AMPK-dependent. The precise mechanisms of 2-AMPK activation by n-3 LC-PUFA as well as downstream effectors of 2-AMPK activation in this context remain to be elucidated.