6 Abstract

Type 2 diabetes mellitus is a complex disease in which genetic and environmental factors interact to produce alterations in insulin secretion and insulin action, leading to an impaired glucose homeostasis. Mice that are double heterozygous for the null alleles of the insulin receptor and the insulin receptor substrate 1 (IR/IRS-1 DH mice) have previously been shown to develop mild insulin resistance, hyperglycemia and hyperinsulinemia due to compensatory ß-cell hyperplasia at the age of six months. Therefore these mice serve as a model for the development of noninsulin-dependent diabetes mellitus (NIDDM).

In this study the IR/IRS-1 DH mice were followed up to the age of twelve months. Surprisingly the IR/IRS-1 DH mice were glucose intolerant only up the age of six months. After that their glucose tolerance improved, returning to the normal level after twelve months. At the same time wildtype mice developed an age dependent progressive glucose intolerance.

Metabolic analysis revealed that the IR/IRS-1 DH mice of all ages show a mild insulin resistance. After six months of age hyperinsulinemia and compensatory ß-cell hyperplasia strongly increased. Wildtype mice showed symptoms of ageing associated type 2 diabetes like declining insulin sensitivity, increasing body fat content and fatty liver. In contrast to this, the IR/IRS-1 DH mice showed a reduced body fat content due to increased energy expenditure despite increased food intake. Moreover the liver of IR/IRS-1 DH mice showed only few lipid inclusions. Therefore the decreased expression of the insulin receptor and IRS-1 seems to have a protective effect against ageing associated type 2 diabetes mellitus.

Western blot analysis of liver, skeletal muscle and white adipose tissue revealed marked differences in amount and phosphorylation of some proteins of the insulin receptor signalling pathway. In white adipose tissue of IR/IRS-1 DH mice the amount of glucose transporters was increased at the age of twelve months, which could indicate an increased glucose uptake leading to the improved glucose tolerance of these animals.

Comparative gene expression analysis based on microarrays of liver and skeletal muscle identified many differentially expressed genes. Some of the differences point to an impaired oxidative phosphorylation in the liver of the IR/IRS-1 DH mice. The altered expression of some genes in skeletal muscle could indicate an improved reaction to ageing associated changes of these animals.