



**Karolinska  
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**Institutionen för Molekylär Medicin och Kirurgi**

# Sex-different control of hepatic metabolism in relation to insulin sensitivity

**AKADEMISK AVHANDLING**

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## ABSTRACT

The liver is a key metabolic organ. The liver has adapted to the different metabolic needs in men and women, and therefore responds in a sex-specific manner to various stimuli. Specific genes have recently been related to the development of hepatic insulin resistance (IR) and with our improved knowledge of sex-differences in fuel metabolism, it may be postulated that the liver has a crucial role in sex-dependent development of IR. To improve the prevention and treatment of hepatic IR, a better understanding of the mechanisms behind sex-differentiated hepatic metabolism is needed. The general aim of this thesis was to investigate if there is a relationship between sex-differences in hepatic fuel metabolism and development of IR.

Sex-differences in hepatic fuel metabolism were characterized in healthy male and female rats (Paper I). Male rats showed higher ratios of insulin to glucagon levels, higher levels of hepatic glycogen, lower degree of hepatic AMPK phosphorylation, higher expression of hepatic gluconeogenic genes and higher hepatic glucose output, as compared to the females. Effects of short-term high-fat feeding on hepatic insulin sensitivity, gene expression, lipid metabolism and plasma lipids in healthy male rats were shown to depend on the lipid source (Paper II). Safflower oil-enriched diet increased hepatic  $\beta$ -oxidation, was beneficial in terms of circulating VLDL-TG, but led to reduced hepatic insulin sensitivity. Cocoa butter-enriched diet did not affect plasma total TG levels, VLDL-TG or hepatic insulin sensitivity. However, effects observed on hepatic gene expression indicated that prolonged cocoa butter feeding might lead to increased lipid synthesis, and concomitant lipotoxicity, inflammation, and IR. The role of hepatic sex differences in metabolic pathways in the development of glucose intolerance and IR was investigated using Zucker diabetic fatty (ZDF) rats (Paper III). It was shown that high-fat feeding in female ZDF rats lead to a more male-like hepatic phenotype, including reduced lipogenesis, increased FA oxidation and ROS production, while glucose intolerance and IR developed. Sex-differences in hepatic metabolic control were also observed at the level of hepatic metabolites (Paper I and III). Metabolite profiles generated from hepatic perfusates from healthy rats using  $^1\text{NMR}$  spectroscopy verified that male livers exported more glucose than females. Liver-derived lactate was also higher in males, and there was a trend towards higher levels of glycerol and glucogenic amino acids. Testosterone treatment in male ZDF rats reduced hepatic fat content but increased blood glucose levels, reduced glucose tolerance and increased circulating levels of TG-rich VLDL particles (Paper IV). Surprisingly, testosterone reduced STAT3 activity, a key mediator of leptin actions in liver and essential for hepatic insulin sensitivity.

Taken together, these findings suggest that the hepatic functions of female rats might contribute to a lower risk of developing lipid-induced oxidative stress and hepatic IR. Observations of key metabolic transcripts suggest that the capacity of females to retain lipogenesis and the secretion of VLDL-TG might be related to this. We speculate that this together with higher rates of FA oxidation and glucose production in males, might at least partly explain why males are more prone to develop insulin resistance, T2D and the metabolic syndrome.