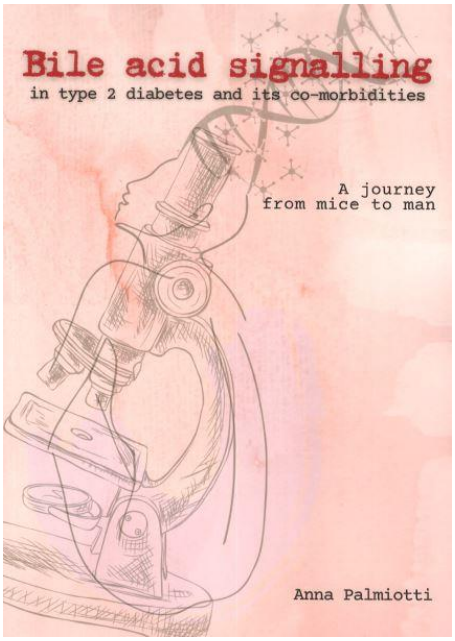

Samenvatting proefschrift
A. Palmiotti

'Bile acid signalling in type 2 diabetes and its co-morbidities: a journey from mice to man'

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Bile acids (BAs) regulate several aspects of metabolism (lipid, glucose, and energy metabolism) by interacting with nuclear (such as FXR/NR1H4) and membrane-bound (such as TGR5/GPBAR1) receptors. BA signalling pathways are increasingly viewed as potential therapeutic targets for a wide range of (metabolic syndrome-related) diseases, including type 2 diabetes (T2D). This dissertation explores the molecular mechanisms by which BAs are causally associated with T2D, insulin resistance (IR), and their co-morbidities and how they may affect metabolic parameters that are frequently dysregulated in these (pathological) conditions. A mouse model with a BA composition similar to that of a human has been created and characterised.

Cyp2c70$^{-/-}$ mice exhibit a sex-dependent cholangiopathy (particularly females). UDCA treatment completely restores the liver phenotype, and BA sequestration with colesevelam ameliorated liver pathology in Cyp2c70$^{-/-}$ mice (without affecting insulin sensitivity), which was accompanied by a decrease in the hydrophobicity of biliary BAs. In regards of human investigations, no associations between BA composition and weight-loss-induced improvements in insulin sensitivity were detected. However, due to the substantial inter-individual variation in BA concentration and composition, subgroup-specific analyses would be useful for the evaluation of future BA-related treatment approaches. In conclusion, the results presented and discussed in this PhD dissertation indicate that BA composition and, consequently, BA hydrophobicity are important and must be considered when interpreting the effects of BAs on glucose metabolism and insulin sensitivity.

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