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Species and strain differences in drug metabolism in liver and intestine

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Species and strain differences in drug metabolism in liver and intestine

Marcella Martignoni

RIJKSUNIVERSITEIT GRONINGEN

Species and strain differences in drug metabolism in liver and intestine

Proefschrift

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Giove padre, deh, togli a questo buio
I figli degli achei, spandi il sereno,
Rendi agli occhi il vedere; e, poiche' spenti
Ne vuoi, ci spegni nella luce almeno.

O father Jove, lift this cloud from over
the sons of the Achaeans; make heaven serene,
and let us see; if you will that we perish,
let us fall at any rate by daylight.

Iliade, Omero

Paranimfen: dr. Inge de Graaf
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Aim of this thesis

During drug discovery and development, potential new medicines can not be administered to humans before extensive metabolic and kinetic studies in animals are performed. However, the question arises whether or not animals are a good metabolic and kinetic model to humans and which species to choose. Therefore, the aim of this research was to study species differences in metabolism and regulation using *in vitro* model systems in combination with sensitive analytical techniques and with analysis of gene expression in order to contribute to the development of better predictive models for the human situation.

Cryopreservation: First cryopreservation of liver slices from the animal species commonly used during drug development (rat, mouse, monkey and dog) and from man was evaluated. We assessed the metabolic capacity of fresh and cryopreserved liver slices after incubation with standard substrates.
In addition, we investigated the differences (qualitative and quantitative) in metabolite profiles among these species (chapter 2).
Induction profile: An important additional objective was the evaluation of the slice model to assess the induction of the main CYPs in liver and intestine in rat and mouse by measuring mRNA expression using real-time RT-PCR and an *in vitro-in vivo* comparison was made (chapter 3 and chapter 4).
Strain differences: A further aim of this thesis was to evaluate possible differences between strains of mice, commonly used in pharmacological studies, which may affect the drug disposition of new chemical entities. Several model compounds were used to characterize phase I and phase II metabolism. In addition, phase III was investigated by measuring the mRNA expression of some important transporters (chapter 5).
Comparison of metabolism in liver and intestine: To explore the relative contribution of liver and intestine, several human CYP3A substrates were incubated with liver and intestinal slices of mouse and rat. The metabolite formation was evaluated by LC-MS/MS. In addition, mRNA expression of different CYP3A isoforms in intestine and liver from mice was evaluated to better understand the role of these organs in CYP3A-mediated metabolism (chapter 6).