Quantitative Systems Toxicology Approach Integrates Simcyp PBPK and Core Hepatocyte Metabolism: a Case Study with Valproic Acid

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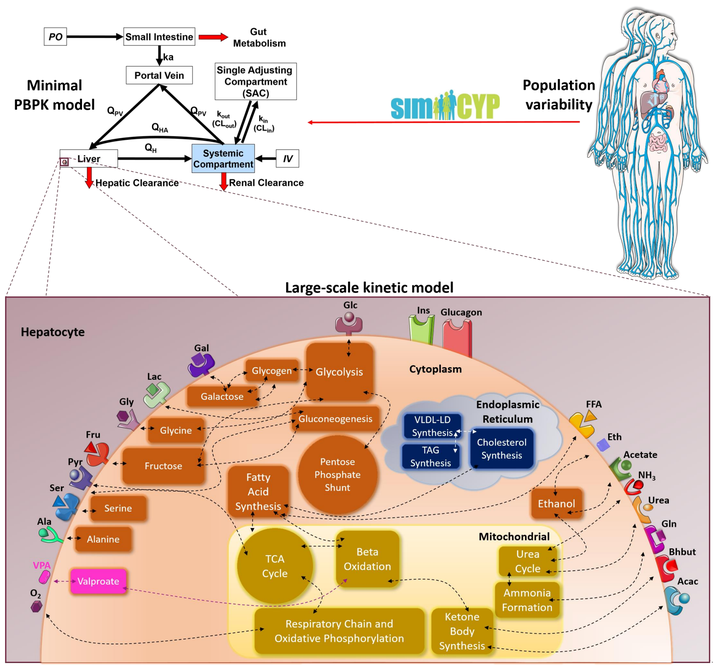
Quantitative systems toxicology modelling approach characterizes effect of **valproic acid** on **lipid metabolism**

transQST

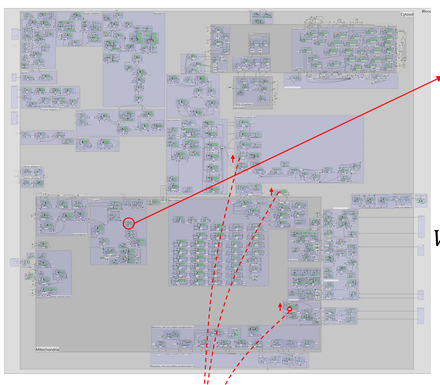
Introduction

- Valproic acid (VPA) is a treatment for epilepsy and bipolar disorder
- A known side effect is induction of hepatic steatosis[1] (lipid accumulation)
- We mechanistically examine and quantify the effect of VPA exposure on lipid metabolism
- We develop a general quantitative systems toxicology (QST) approach integrating Simcyp PBPK with core hepatic metabolism[2] regulated by PPARα and insulin signalling

Multi-scale QST model

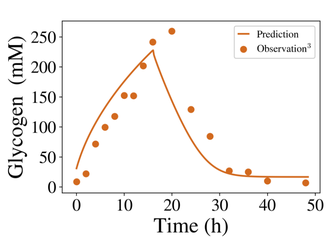


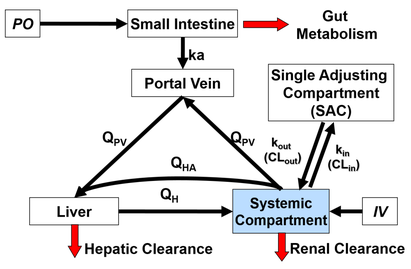
Schematic representation of QST approach

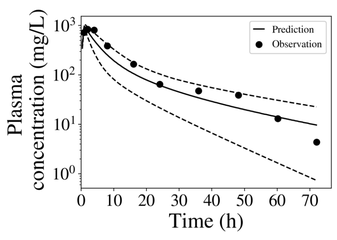


$$V_{AC} = \frac{V_{max}^{AC}(cit_{mito} - \frac{iscoit_{mito}}{K_{eq}^{AC}})}{(1 + \frac{cit_{mito}}{K_m^{citmito}} + \frac{isocit_{mito}}{K_m^{isocitmito}})}$$

PPARα controlled reactions



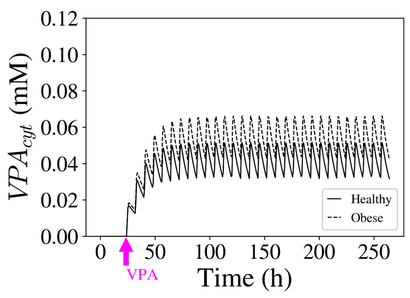




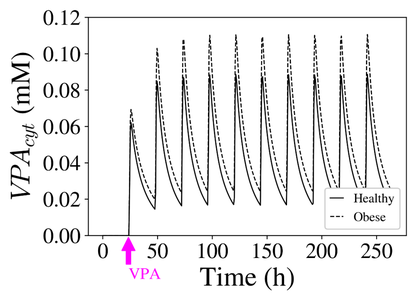
Models are verified independently

Liver concentration of VPA

Oral dose: 250 mg (τ = 8h)

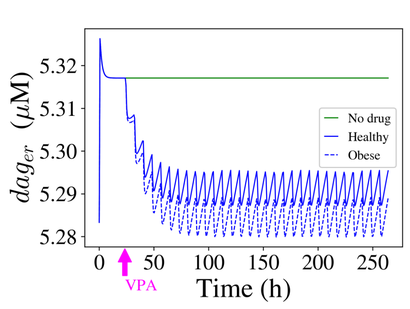


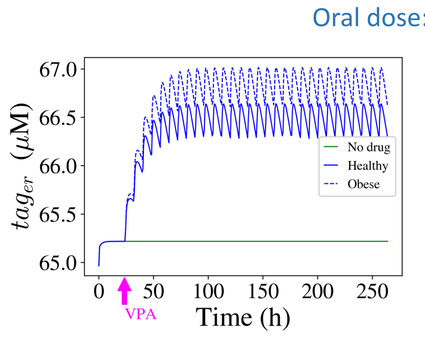
Oral dose: 750 mg (τ = 24h)



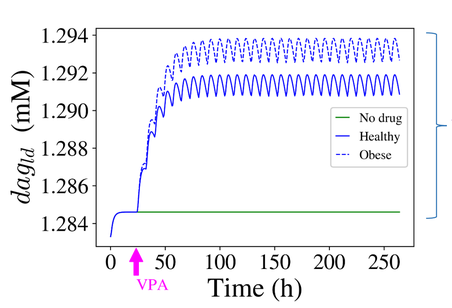
Effect of VPA on lipid metabolism

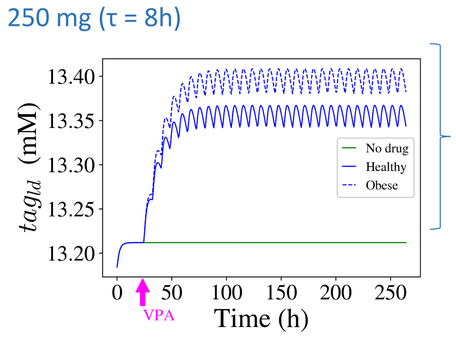
Endoplasmic reticulum





Lipid droplet



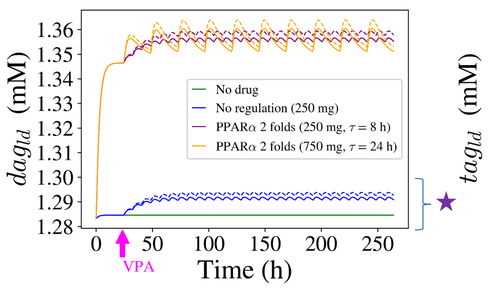


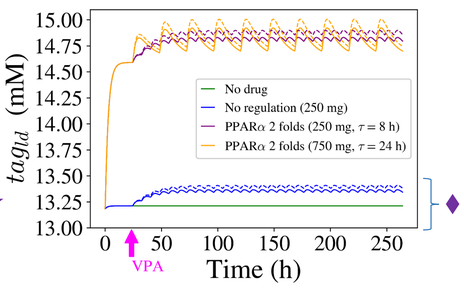
VPA causes persistent disturbance in lipid metabolism

Effect of PPARα on lipid metabolism

- PPARα is a key regulator of fatty acid metabolism

- Healthy -- Obese





PPARα regulation enhances the effect of VPA

Discussion

- We developed a general QST modelling approach to evaluate liver toxicity
- We identify that chronic treatment with VPA results in a persistent disruption in lipid metabolism
- We explore the impact of lipid dysregulation in obese individuals
- We are further evaluating how PPARα regulation affects lipid concentration

Additional Information

Reactions regulated by PPARα[4]

Enzyme	Reaction
AAT	$akg_{cyt} + ala_{cyt} \longrightarrow glu_{cyt} + pyr_{cyt}$
ACC1/ACC2	$acoa_{cyt} + atp_{cyt} \longrightarrow adp_{cyt} + p_{cyt} + malcoa_{imm}$
ACSL1/ACSL4/ACSL5	$atp_{cyt} + c16_{cyt} + coa_{cyt} \longrightarrow amp_{cyt} + c16coa_{cyt} + pp_{cyt}$
ALDR	$gra_{cyt} + nadph_{cyt} \longrightarrow glyc_{cyt} + nadp_{cyt}$
ALDDHI/ALDDHII	$aald_{cyt} + nad_{cyt} \longrightarrow acetate_{cyt} + nadh_{cyt}$
$ALDDH_{gra}$	$gra_{cyt} + nad_{cyt} \longrightarrow glycerate_{cyt} + nadh_{cyt}$
ASL	$arg\_succ_{cyt} \longrightarrow arg_{cyt} + fum_{cyt}$
CACT	$c16car_{cyt} + car_{mito} \longrightarrow car_{cyt} + c16car_{mito}$ $valcar_{cyt} + car_{mito} \longrightarrow car_{cyt} + valcar_{mito}$
CPS	$2\ atp_{mito} + NH_{3_{mito}} \longrightarrow 2\ adp_{mito} + cmp_{mito} + p_{mito}$
CPT1	$c16coa_{cyt} + car_{cyt} \longrightarrow c16car_{cyt} + coa_{cyt}$ $valcoa_{cyt} + car_{cyt} \longrightarrow valcar_{cyt} + coa_{cyt}$
$G6P_{er}$	$glc6p_{er} \longrightarrow glc_{er} + p_{er}$
Glyck	$atp_{cyt} + glyc_{cyt} \longrightarrow adp_{cyt} + g3p_{cyt}$
GLNASE	$gln_{mito} \longrightarrow gln_{mito} + NH_{3_{mito}}$
HMG_{syn_cyt}	$acoa_{cyt} + kc4coa_{cyt} \longrightarrow coa_{cyt} + hmgcoa_{cyt}$
HMG_{syn}	$acoa_{mito} + kc4coa_{mito} \longrightarrow coa_{mito} + hmgcoa_{mito}$
ME	$mal_{cyt} + nadp_{cyt} \longrightarrow nadph_{cyt} + pyr_{cyt}$
OTC	$cmp_{mito} + orn_{mito} \longrightarrow ctl_{mito} + p_{mito}$
PEPCK	$gtp_{cyt} + oaa_{cyt} \longrightarrow gdp_{cyt} + pep_{cyt}$

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