A Physiologically Based Pharmacokinetic and Pharmacodynamic Model of Lixisenatide

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BACKGROUND

This project leverages an open pharmacokinetics database, along with established data curation and model simulation protocols, to develop a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model for the GLP-1 receptor agonist lixisenatide. Since type 2 diabetes mellitus (T2DM) is often accompanied by liver and renal impairments, obesity, and cardiovascular disease, this study aims to assess how these factors influence drug behavior. By developing a PBPK/PD model, we aim to establish a tool to support personalized medicine of T2DM management.

METHODS

Over 50 publications on lixisenatide pharmacokinetic (PK) and pharmacodynamic (PD) were identified through a systematic literature review using PubMed and the PKPDAI database. Relevant studies were selected for curation and uploaded into PK-DB.

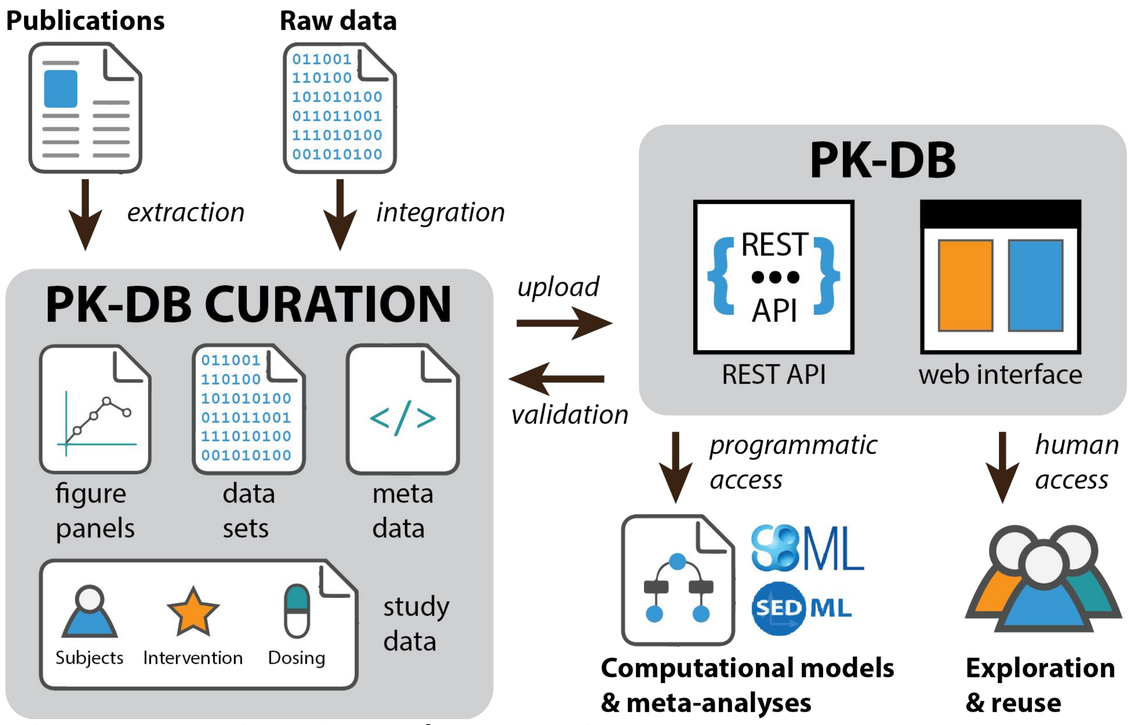

Figure 1. Overview of PBPK/PD modelling methodology.

The PBPK/PD model was developed using a compartmental approach and encoded in Systems Biology Markup Language (SBML) to ensure accessibility and reproducibility. Model optimisation was performed through parameter fitting to maximize agreement between experimental observations and model predictions.

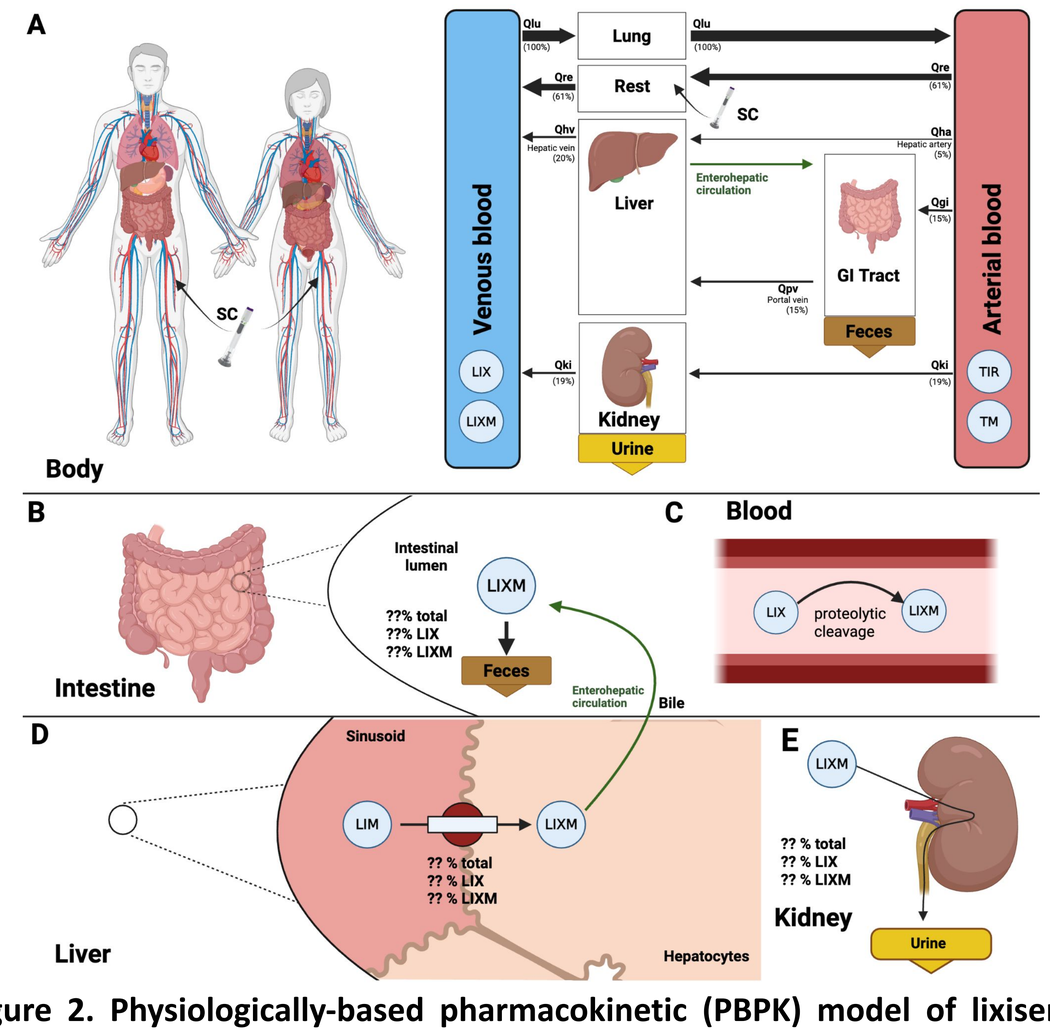

Figure 2. Physiologically-based pharmacokinetic (PBPK) model of lixisenatide. (A) Overview of PBPK lixisenatide (LIX) model. **(B)** Intestinal absorption of LIX. **(C)** Blood compartment showing proteolytic cleavage of LIX into LIXM. **(D)** Hepatic metabolism in the liver. **(E)** Renal excretion of LIX and LIXM, with concentrations and pathways remaining unclear due to limited data.

RESULTS

Study Identifier	Data		Curation					Health						PK	PD							
Study	pk	pd	docs	repo	upload	simulation	fitting	healthy	diabetes	overweight	renal	hepatic		plasma/serum lixisenatide	bodyweight	C-Peptide	Fasted Glucose	Glucagon	HbA1c	Insulin	PPG	
Ahren2013	-	☑	☐	☐	☐	☐	☐	-	☑	☑	-	-	-	-	-	-	☑	-	☑	-	-	
Barrientos-Perez2022	☑	☑	☑	☑	☑	☑	☐	☑	-	-	-	-	-	☑	☑	-	☑	☑	☑	☑	-	
Becker2014	☑	☑	☑	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	☑	☑	☑	-	☑	-	
Becker2015	☑	☑	☑	☑	☑	☑	☑	☑	☑				-	☑	-	☑	☑	☑	-	☑	-	
Raccah2015	☑	☑	☑	☑	☑	☑	☐	☑	-	-	-	-	-	☑	-	-	-	-	☑	-	-	
FDA review document	☑	☑	☐	☑	☑	☐	☐	☑	☑	☑	☑	☑	☑	☑	☑	-	☑	☑	☑	☑	☑	
Pinget2013	-	☑	☑	☑	☐	☑	☐	-	☑	☑	-	-	-	-	-	-	☑	-	☑	-	-	
Rayner2020	-	☑	☑	☑	☑	☐	☐	-	☑	-	-	-	-	-	☑	☑	☑	☑	☑	☑	☑	
Riddle2013	-	☑	☑	☐	☐	☐	☐	-	☑	☑	-	-	-	-	☑	-	☐	-	☑	☑	-	
Riddle2013a	-	☑	☑	☑	☑	☐	☐	-	☑	☑	-	-	-		☑		☑		☑	☑		
Rosenstock2013	-	☑	☑	☑	☑	☐	☐	-	☑	☑	-	-	-	-	☑	-	☑	-	☑	-	-	
Rosenstock2014	-	☑	☑	☐	☐	☐	☐	-	☑	☑	-	-	-	-	-	☑	-	☑	☑	☑	☑	
Xie2023	☑	-	☑	☑	☑	☑	☑	☑	-	-	-	-	-	☑	-	-	-	-	-	-	-	

Figure 3. Overview of curated studies and available data for lixisenatide PBPK/PD modeling. This table summarizes data availability and processing across studies included in the model development.

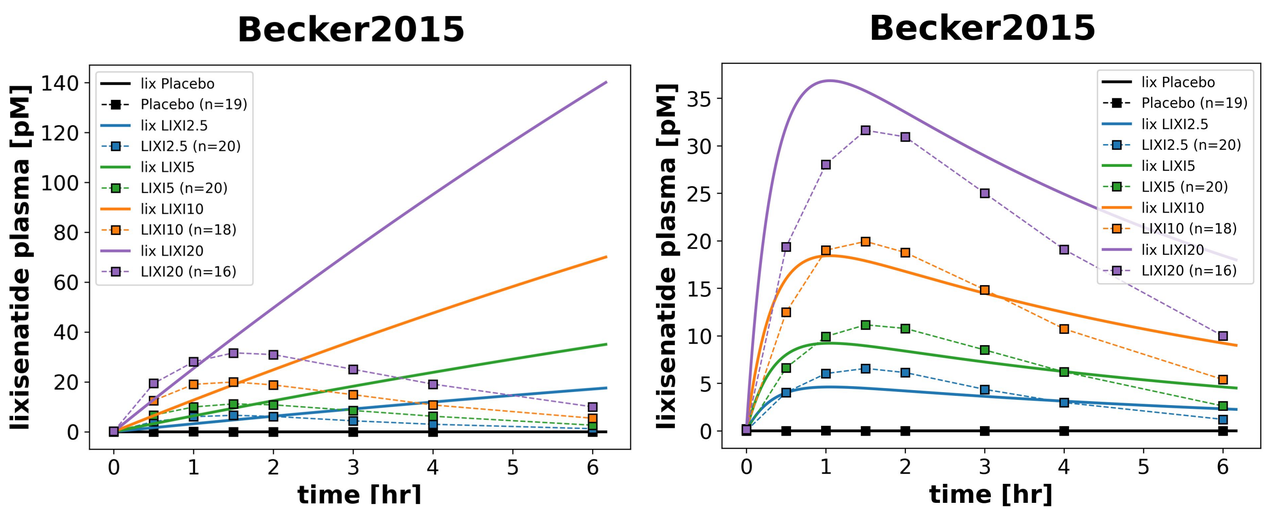

Figure 4. PK model simulation and predictions before and after parameter optimization. Solid lines represent model predictions, while dotted lines correspond to experimental data (mean ± SD).

FUTURE DIRECTION

With the PK part of the project nearing completion, we will now shift our focus to the PD aspect. Given lixisenatide's ability to manage postprandial hyperglycemia (PPG) more effectively than current longer-acting options, our primary focus will be on its effects on gastric emptying and PPG control. This next phase will involve identifying existing mathematical models and experimental time-course data to model these PD effects and incorporating them into the PBPK model to further enhance our understanding of lixisenatide's pharmacological profile.

HUMBOLDT INTERNSHIP PROGRAMME (HIP) EXPERIENCE

The Humboldt Internship Program has been an eye-opening experience, providing me with valuable insights into the intersection of computational tools and pharmacology. Through this project, I have learned how to simulate the effects of a heterogeneous disease on drug metabolism, which has deepened my understanding of pharmacogenomics and personalized medicine. I am excited to see how the concepts and skills I have gained during this internship can be applied to future research. Thank you Dr. König for your guidance and patience throughout this research project. The passion you put into your research continuously inspires me and I will ensure to carry your teachings with me through my research career.

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