Incorporation of Renal SGLT Function into a Quantitative Systems Pharmacology (QSP) Model

Mike Reed1, Michael Weis2, Rebecca Baillie1, Hans-Christoph Schneider2, Thomas Klabunde2
1Rosa & Co., LLC, San Carlos, CA; 2Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany.

Introduction

• Sodium-glucose cotransporters (SGLT1 & SGLT2) absorb glucose from the renal filtrate into the plasma and SGLT1 absorbs glucose in the GI tract.
• Inhibition of SGLTs reduces plasma glucose and is a successful therapeutic approach for type 2 diabetes (T2D).
• SGLT inhibitors (SGLTI) targeting both SGLT1 and SGLT2 may overcome the adaptation found with SGLT2 inhibition (Figure 4).

Objective

• Investigate the relative contributions of SGLT1 and SGLT2 to kidney glucose reabsorption.

Methods

Mechanistic, quantitative systems pharmacology models elucidate the connection between mechanisms and outcomes.

• A PhysioPD™ Research Platform is a graphical, mathematical QSP model of biology developed in SimBiology® combining engineering approaches and scientific data analysis to clarify complex physiology and drug interactions.
• Rosa developed the SGLT QSP model integrating plasma glucose, glomerular filtration rate (GFR), and SGLT1 and SGLT2 function in the first three segments of the proximal tubule to explore the impact of alternative SGLTIs on urinary glucose excretion (UGE).
• The SGLT Platform was qualified in accordance with Rosa’s Model Qualification Method (MQM) (Figure 1).
• Healthy (HVP) and diabetic (DVP) virtual patients were developed to examine the effects of SGLT1 and SGLT2 co-inhibition.

Results

Renal SGLT function was incorporated with glucose metabolism.

• The Platform included representation of the first three segments of the proximal convoluted tubule (PCT) (Figure 2).
  o GFR regulates the flow of plasma to the PCT
  o Outputs in the Platform include plasma glucose and urine glucose
  o SGLT2 and SGLT1,2 regulate the flow of glucose from PCT to plasma
  o Plasma glucose metabolism was incorporated as a separate Platform module

Platform Results

The Platform includes a simplified representation of renal glucose transport

UGE is dependent on the activity of SGLT1, SGLT2, GFR and fasting and mean plasma glucose.

Preclinical VPs were used to explore mechanistic uncertainties.

• Investigate the impact of variability key pathways of interest:
  • Explore interactions between kidney function and drug effects
  • Explore interactions with fasting glucose
  • Explore variability around drug function

Table 1. VP characteristics

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<th>Virtual Patient</th>
<th>FPG</th>
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<th>HOMA-IR</th>
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The effect of SGLT1 inhibition alone on UGE is minor but may be significant with co-inhibition of SGLT2.

Conclusions

• Co-inhibition of SGLT1 and SGLT2 may be an effective treatment for T2D with drug efficacy dependent the balance of SGLT1 vs. SGLT2 inhibition, kidney function and plasma glucose concentration.

References


For more information about this work, please contact Mike Reed Rosa & Co. LLC (503) 933-3718 mreed@rosaandco.com