IMPACT OF MODELING ON GPR119 AGONIST DEVELOPMENT

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OBJECTIVES & BACKGROUND

GPR119 is a G protein-coupled receptor expressed in beta cells in the pancreas and L cells in the gastrointestinal tract in humans. Activation of the GPR119 receptor causes an increase in intracellular cAMP levels via adenylate cyclase resulting in GLP-1 release from L cells and insulin release by the pancreas. Thus, GPR119 agonists are potential candidates for diabetes therapeutics and are being developed as such by several companies. However, some important aspects of the mechanism of action of GPR119 agonists are unresolved by current data. For example: How much production and release of GLP-1 can be induced by GPR119? Since GLP-1 also increases glucose stimulated insulin release, is there an interaction between the GPR119 and GLP-1 signaling pathways in pancreas which would limit insulin release? Does GPR119 slow down gastric emptying either directly or through GLP-1 release?

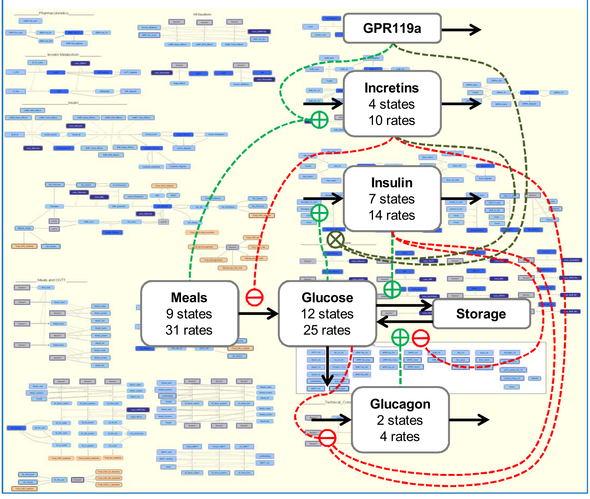
We chose to develop a model of GPR119 physiology and pharmacology in relationship to diabetes to address these and other decisions within a GPR119 program. We wanted to understand the relative contributions of direct and indirect action of GPR119 agonists on glucose control, and thus, identify a chemical strategy that maximized efficacy and/or better differentiated GPR119 compounds from competitors. The current model will be used to translate preclinical data to simulate and predict human clinical response, to optimize dose selection and to enhance the designs of the First-in-human, Proof of Mechanism, and Proof of Concept studies with quantitative go/no go criteria for GPR119-based therapies.

METHODS

We developed a Physiologically-based model which includes insulin, glucose and glucagon metabolism as well as GPR119 MOA and efficacy measures. Meals, infusions, and the physiology and pharmacokinetic models for sitagliptin, exenatide, metformin, and glyburide were also included in the model as both test measures for the model itself, and as comparators for GPR119 agonist compounds. Detailed incretin metabolism and effects were included in this model and will be detailed in this presentation. The model structure and parameters for GLP-1 production, degradation, and metabolic effects were developed and tested based on literature data, specifically targeting the sitagliptin and exenatide literature. The parameters were then further refined using publically available data for GPR119 agonists. [1,2] Mechanisms were included to address a number of hypotheses for GPR119 effects in gastric emptying and GLP-1 release. Pharmacokinetic information for GPR119 in the model incorporated a PK model, as well as a variety of compound-specific parameters such as potency, intrinsic activity, bound fraction, and molecular weight, to permit easy testing of new compounds and definition of new compound characteristics for medicinal chemistry.

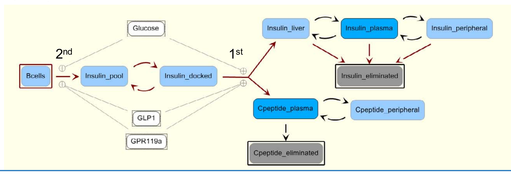
Pfizer-Rosa physiological model of diabetes

The model represents the physiology, pathophysiology, and pharmacology relevant to GPR119 agonism. The model is comprised of multiple interconnected modules which describe: 1) glucose distribution, storage and utilization; 2) insulin secretion, distribution and elimination; 3) incretin secretion, distribution and elimination; 4) glucagon secretion, distribution and elimination; 5) nutrient absorption (*e.g.* meals) and glucose perturbations (*e.g.* OGTT); and 6) pharmacokinetics and pharmacodynamics of relevant antidiabetic therapeutics (*e.g.* sitagliptin, exenatide, metformin, and glyburide).



Insulin Module

For example, the insulin module produces insulin from ß-cells into a storage pool that equilibrates with docked readily releasable insulin. Glucose stimulated insulin secretion (GSIS) occurs in two phases: immediate release of docked insulin (1st phase) and prolonged secretion (2nd phase) as a function of increased production. Both phases of GSIS can be additionally potentiated by GLP-1 and GPR119 receptor agonism. Insulin then partitions between liver, plasma, and peripheral tissues from which it is eliminated.



RESULTS

- Key metabolites and hormones included in model were glucose, lactate, multi-phase insulin and C-peptide release, incretins and glucagon.
- Maintenance of energy balance was a primary constraint of the model.
- The contributions of GLP-1 production, direct insulin release, and potential gastric emptying effects to GPR119 agonist efficacy were quantitatively tested in the model and the results compared to publically available data.
- An extensive set of tests were performed and documented to ensure the model was suitable for purpose.
- The potential efficacy and required dose levels of partial and full agonist compounds were evaluated.

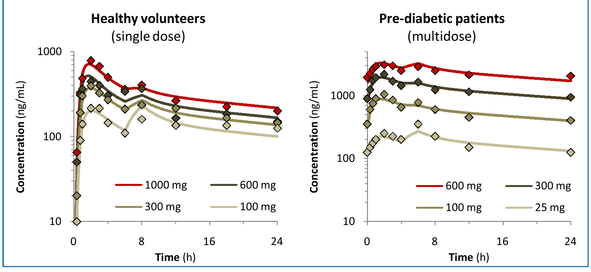
CONCLUSIONS

- Direct effects on GLP-1 release with resulting insulin production or direct effects on insulin production appear to have approximately equal contributions to GPR119 agonist efficacy on glucose homeostasis.
- GPR119 agonism having no direct effect on gastric emptying is consistent with data and modeling analysis, and the indirect effect through GLP-1 appears to be very limited.
- The model can be used to evaluate the degree of partial agonism that would yield an acceptable compound.
- While GPR119 agonists have potential as diabetes therapeutics, both increased direct insulin release and increased GLP-1 release would be necessary to achieve marketable therapeutic potential.

REFERENCES

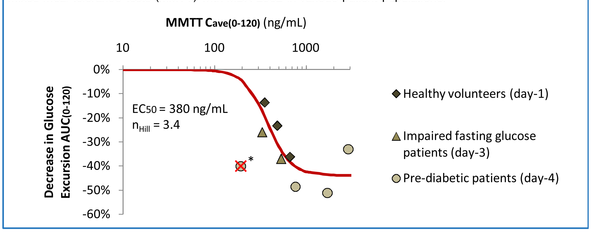
1. Roberts, B., et al. (2009). "American Diabetes Association 69th Annual Scientific Sessions," New Orleans, LA, USA, 5–9 June, Abstract 164-OR.
2. Roberts, B., et al. (2010). "American Diabetes Association 70th Annual Scientific Sessions," Orlando, FL, USA, 25–29 June, Abstract 603-P.
3. Frank T. Bergmann, Herbert M. Sauro. SBW - a modular framework for systems biology. Frank T. Bergmann, Herbert M. Sauro December 2006 Proceedings of the 37th conference on Winter simulation WSC '06 Publisher: Winter Simulation Conference Pages: 1637 – 1645

MBX-2982 clinical pharmacokinetics [1,2]



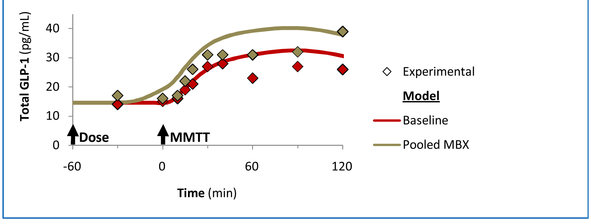
GPR119a glucose lowering concentration–effect relationship [1,2]

Both sites of GPR119 agonism (ß and L cells) were assumed to have equivalent potencies (EC_{50}) and Hill coefficients (n_{Hill}) based on the below clinical concentration-effect relationship of glucose lowering during mixed meal tolerance tests (MMTT) with MBX-2982 in various patient populations.



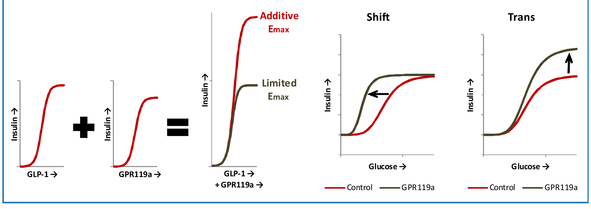
GPR119a mediated GLP-1 secretion [1]

GPR119 agonism is predicted to maximally stimulate basal incretin secretion by 1.8-fold based on the observed postprandial elevation in total GLP-1 during a MMTT following a single dose of MBX-2982 in healthy volunteers (pooled 300, 600, & 1000 mg).



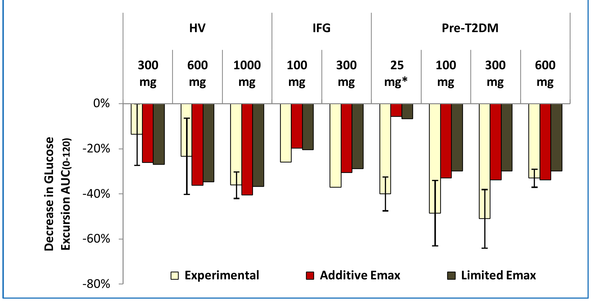
GPR119a mediated insulin secretion

The interaction between GPR119a and GLP-1 on signaling pathways of insulin secretion in the pancreas was investigated assuming no interaction (*i.e.* additive E_{max}) or their combined maximal effect limited to that of GLP-1 (*i.e.* limited E_{max}). Experiments with preclinical rat islets demonstrated that GPR119 agonism both left-shifts glucose stimulated insulin secretion (GSIS) and increases maximal secretion.



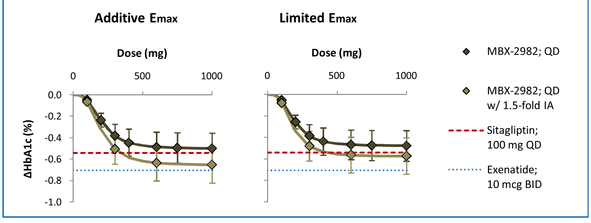
MBX-2982 MMTT glucose lowering [1,2]

Glucose lowering not accounted for by GPR119a mediated incretin secretion was explained through direct stimulation of insulin secretion.



MBX-2982 projected HbA1c lowering in virtual diabetic patients

Projection of MBX-2982 steady-state HbA1c lowering was explored in a group of virtual diabetic patients (VP, n=43) with mean initial HbA1c of 8.7%. MBX-2982 is predicted to maximally reduce HbA1c slightly less than achievable with sitagliptin (100 mg QD). To achieve comparable or greater HbA1c lowering than sitagliptin, a GPR119 agonist with greater intrinsic activity (IA) relative to MBX-2982 would be necessary.



Contributions of GPR119a effects on HbA1c lowering

Individual contributions GPR119a effects on steady-state HbA1c lowering were explored in the diabetic VPs with MBX-2982 (1000 mg QD).