Adapting a quantitative systems toxicology model of mitochondrial dysfunction in liver to kidney

Shailendra B. Tallapaka, Yeshitila Gebremichael, Scott Q. Siler, Brett A. Howell, Jeffrey L. Woodhead

DILIsym Services, Inc., a Simulations Plus Company, Research Triangle Park, NC

ABSTRACT

Objective: Kidney, as a major excretory organ, is exposed to high levels of drugs and their metabolites. Therefore, kidney toxicity is an important part of drug safety assessment in clinical trials. RENAsym™ is a quantitative systems toxicology (QST) model of drug induced acute kidney injury (AKI) currently under development. In its current form, the model includes representations of proximal tubule cell (PTC) lifecycle, bioenergetics, cellular injury and death pathways. Our objective is to develop a mechanistic mathematical model of mitochondrial dysfunction in proximal tubule cells to predict drug induced AKI.

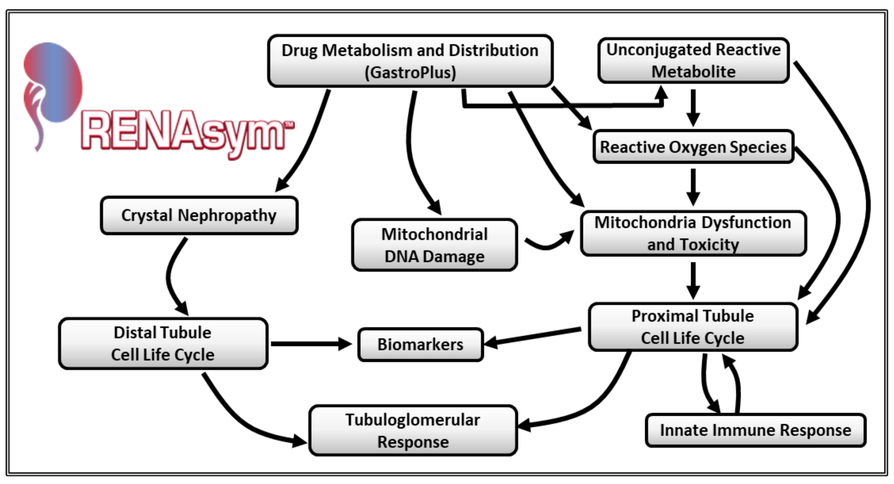
Methods: We adapted the mitochondrial dysfunction model existing in DILIsym®, a QST model of drug induced liver injury, by modifying the equations to accommodate the physiological differences between kidney and liver. Changes made in order to translate the model to the kidney include (but are not limited to) eliminating de novo lipogenesis and glycogen storage, refining PTC bioenergetics, and changing mitochondrial substrate utilization. For example, glucose oxidation was removed during homeostasis as little glucose oxidation was observed in rat proximal convoluted tubules. We then simulated gentamicin as an exemplar compound to qualitatively validate the model. Gentamicin in vitro mitochondrial toxicity was measured in HepG2 cells and converted to RENAsym™ parameters using MITOsym®. Parameters for oxidative stress and kidney exposure were obtained from literature.

Results: Simulations predicted significant toxicity in rats (100 mg/kg QD dosing) and humans (3mg/kg QD dosing) within 24h. Oxidative stress was predicted to be the major mechanism of toxicity in both species. Mild mitochondrial signals were predicted in rats and none in humans.

Conclusions: A mitochondrial dysfunction model originally constructed for the liver has been adapted to the kidney and reasonably predicts gentamicin-induced AKI. Simulations show that gentamicin induced oxidative stress causes more toxicity than mitochondrial dysfunction.

INTRODUCTION

- Over the counter and prescription drugs with kidney liabilities are implicated in 17-26% of acute kidney injury cases in the clinic[1].
- Drug induced acute kidney injury is also one of the leading causes of safety related attrition during drug development.
- RENAsym™ is a quantitative systems toxicology model of drug induced acute kidney injury currently under development, which upon completion would include mitochondrial dysfunction, oxidative stress, DNA depletion/damage, and crystal nephropathy as mechanisms of tubular injury.
- In RENAsym™, drugs can be modeled to cause mitochondrial dysfunction by uncoupling mitochondria, inhibiting electron transport chain activity, or depleting mitochondrial DNA.
- In the first phase of RENAsym™ development Gentamicin was used as positive control exemplar compound.
- Gentamicin is a widely used aminoglycoside antibiotic for the treatment of gram-negative bacterial infections, that is known to cause acute kidney injury in ~24% of patients.

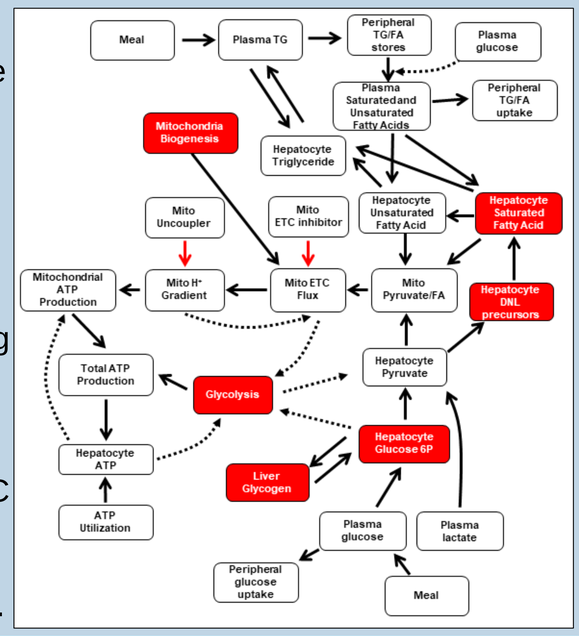


Scan or visit URL to get poster download!

simulations-plus.com/st1

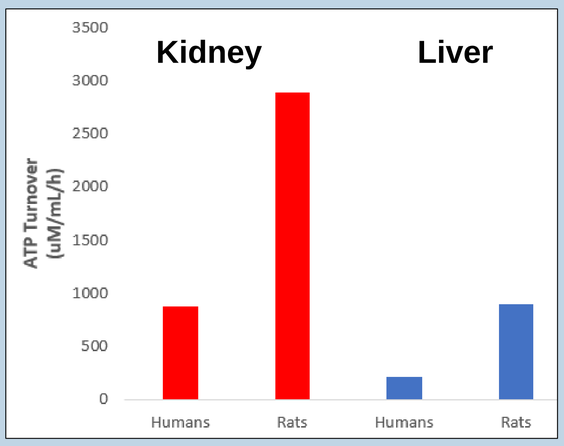
METHODS

- Mitochondrial dysfunction sub-model in RENAsym™ representing proximal tubule cell bioenergetics and substrate utilization was adapted from DILIsym® by removing specific processes(red bubbles) and reparametrizing the model based on published kidney energetic needs.
- Gentamicin plasma and kidney cortex profile for rats was extracted from literature[2] and scaled for higher doses.
- Gentamicin plasma profile for humans was extracted from clinical data [3] and kidney cortex profile was estimated using scaling factor derived from rats.
- MITOsym®, a model of in vitro mitochondrial bioenergetics, was used to fit mitochondrial toxicity data measured in HepG2 cells and conversion factors were used to derive ETC inhibition parameters for RENAsym™.
- Gentamicin induced oxidative stress parameters were optimized based on normalized ROS at a single exposure[4].

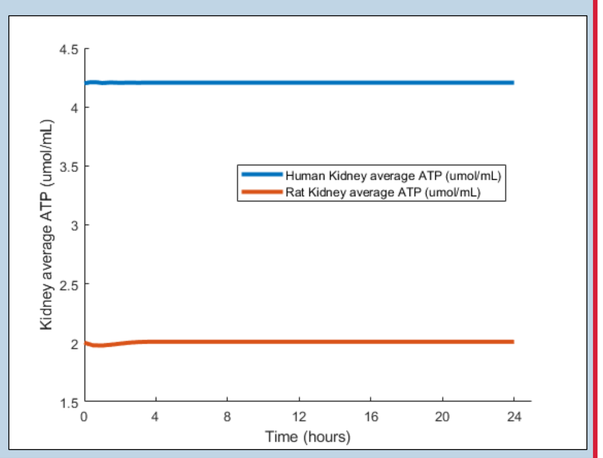


RESULTS

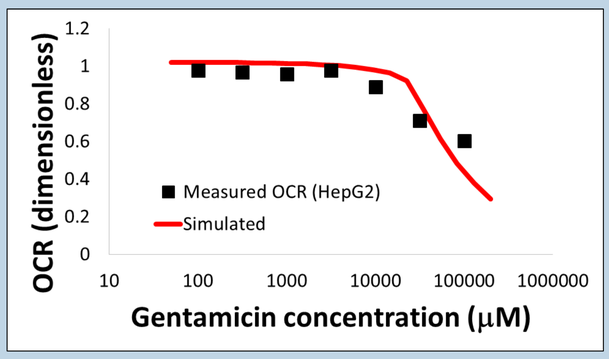
Steady State Simulations



RENAsym has been parameterized to capture the high ATP turnover rate observed in the kidney (left) when compared to liver and can maintain average ATP levels at steady state (right).



Invitro Toxicity



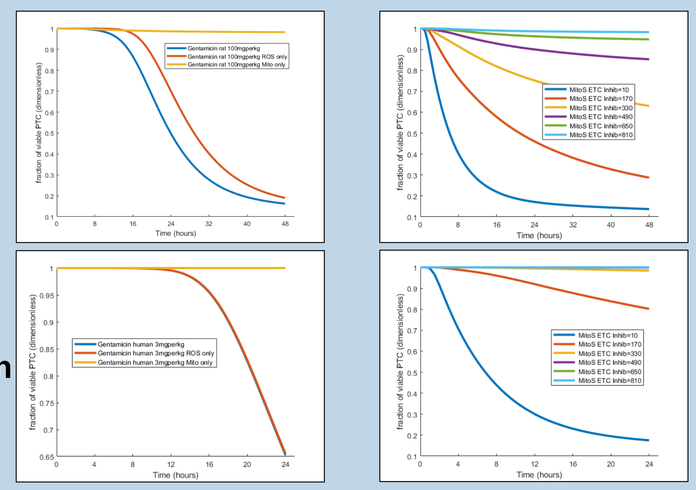
RENAsym Parameter	Value from HepG2 data (mM)	Species	Conversion factor	Parameter Value (mM)
ETC inhibition coefficient 1	8100	Rat	0.1	**810**
		Human	1.0	**8100**

Gentamicin ETC inhibition was measured in HepG2 cells and was fit using MITOsym®. ETC inhibition coefficient calculated in MITOsym was converted to RENAsym™ parameter using rotenone-derived conversion factor

Toxicity Simulations

Rat

Human



Simulations in rat (Top left) and human (Bottom left) predicted significant toxicity within 24 h. Experimental data show that moderate toxicity is observed in rats[5] and humans [6] at the simulated doses suggesting the simulations overpredicted toxicity. Oxidative stress was predicted to be the dominant mechanism in both species. Sensitivity analysis predicted rats (Top right) to be more sensitive to gentamicin induced ETC inhibition than humans (Bottom right)

CONCLUSION

- A QST model of mitochondrial dysfunction in liver was adapted to represent kidney.
- RENAsym™ successfully predicted gentamicin induced AKI in both humans and rats. However, severity was over predicted.
- Oxidative stress was predicted to be major driver in gentamicin induced AKI.

ACKNOWLEDGEMENTS

- Dr. Melissa Hallow and Dr. Zheng Dong
- This work was supported by the NIDDK of NIH grant R44DK118981.
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Uchino S et al JAMA. 2005 Aug 17; 294(7):813-8.
2. Fabre J et al Kidney International, Vol. 10 (1976), p. 444—449
3. Chung M et al, Antimicrobial Agents and Chemotherapy, Feb. 1980, p. 184-187
4. Martinez-Salgado et al, Kidney International, Vol. 62 (2002), pp. 1682–1692
5. Hosaka et al. (2004) Braz J Med Biol Res 37:979-985
6. SelbyNM et al Q J Med 2009; 102:873–880

RENAsym™ DILIsym Services

A SIMULATIONS PLUS COMPANY