Mechanistic Representation of NAG Release in Relation to Renal Proximal Tubular Cellular Injury

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INTRODUCTION

- Novel Acute kidney injury (AKI) biomarkers enhance disease understanding and aid timely interventions.
- N-acetyl-beta-D-glucosaminidase (NAG) is a novel biomarker which is released in the urine due to proximal tubular damage[1].
- While elevated levels of NAG in urine have been associated with renal tubular cell breakdown, the mechanistic underpinnings of NAG release remain poorly understood.

OBJECTIVE

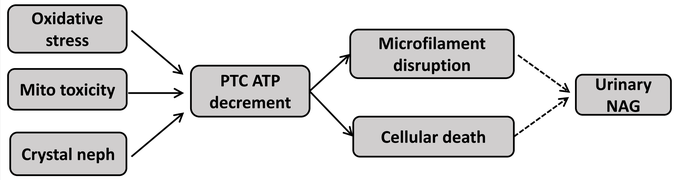
- The aim of this study is to investigate the relationship between NAG release and potential mechanisms of proximal tubular injury, and to identify a responsible mechanism to guide NAG release during AKI.

METHODS

- We developed a mathematical model of NAG release from proximal tubule cells (PTCs) within the framework of RENAsym, a quantitative systems toxicology model of drug-induced AKI.
- The model was designed to represent urinary NAG increase as a result of cellular necrosis or sublethal injury in the form of brush border loss.
- In RENAsym, ATP decline results in various forms of cellular injury including microfilament disruption, brush border loss and cellular necrosis.
- NAG release was simulated using a driving signal from either necrosis or microfilament disruption and parameterized using observed urinary NAG in rats treated with cisplatin[2] and Cyclosporine A (CsA)[3].

MECHANISTIC MODEL OF NAG RELEASE

- Two hypotheses for NAG release were investigated:
  - NAG shedding driven by microfilament disruption and brush border loss[4] (microfilament disruption already represented in RENAsym[5])
  - NAG shedding driven by cellular death in the form of necrosis[1]

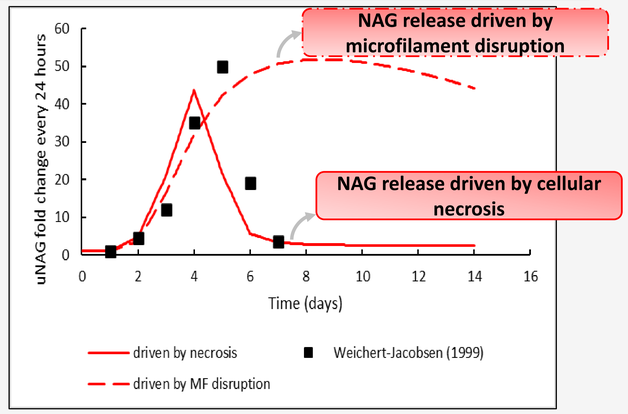


RESULTS

- Data shows that urinary NAG (uNAG) peaked on day 5 in rats treated with 5 mg/kg cisplatin[2]
- In our model, when uNAG release is connected to microfilament disruption, simulated uNAG peaks around day 10 with a slow decay post-treatment with 5 mg/kg cisplatin
- However, when uNAG release is driven by necrosis, simulated uNAG peak time occurs on day 5 consistent with observations
- The model was then calibrated to AstraZeneca's biomarker data instead of uNAG in cisplatin-induced AKI rats
  - Simulated uNAG peak time occurs on day 5 or 6 with maintained elevation until day 14 after administration of daily dosing of CsA into rats for two weeks
- Predicted uNAG for rats treated with 5 mg/kg cisplatin with the optimized model is within the wide range of observed data [3,6-7], peaked on day 4 and resolved within 48-72 hours

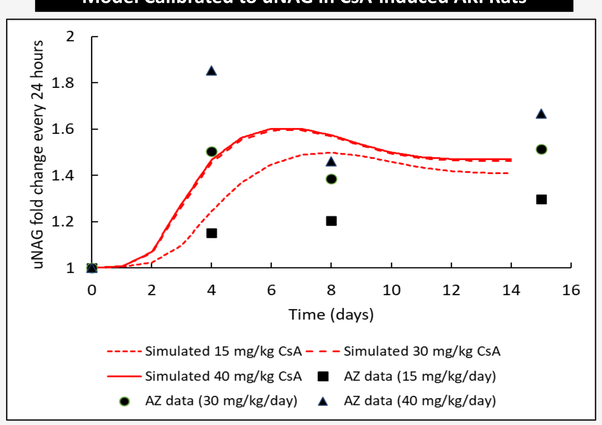
Simulated an Individual Rat with 5 mg/kg Single Dose of Cisplatin

Model *initially* Calibrated to uNAG in Cisplatin-induced AKI Rats



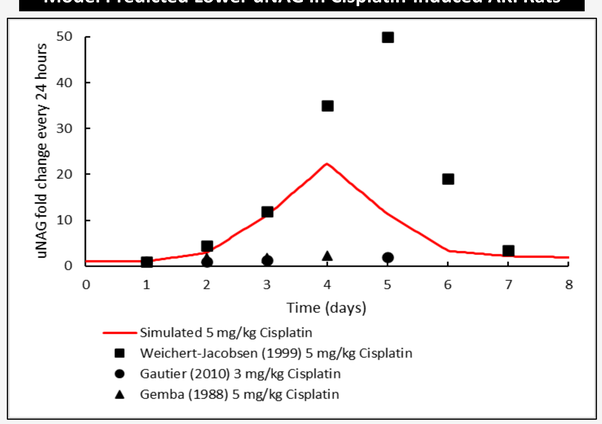
Simulated an Individual Rat with Multiple Doses of CsA for Two Weeks

Model Calibrated to uNAG in CsA-induced AKI Rats



Simulated an Individual Rat with 5mg/kg Single Dose of Cisplatin

Model Predicted Lower uNAG in Cisplatin-induced AKI Rats



CONCLUSION

- In this urinary NAG release model, cellular necrosis is found to be the correct mechanism to drive NAG release, and to successfully reproduce the NAG time course during drug-induced AKI.
- The model could recapitulate the timing of observed NAG levels in cisplatin-induced injury in rats, and NAG kinetics in CsA-induced injury in rats.
- High mortality rate in rats treated with 5 mg/kg cisplatin raises doubts in biomarker data collected after day 5 post-treatment with cisplatin.
- A virtual population model can effectively capture interpatient variability by varying and combining pathophysiologic parameters across a spectrum of baseline individuals.

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