Department of Physiology and Pharmacology

Decreased Nuclear Receptor Activity Mediates Downregulation of Drug Metabolizing Enzymes in Chronic Kidney Disease Through Epigenetic Modulation

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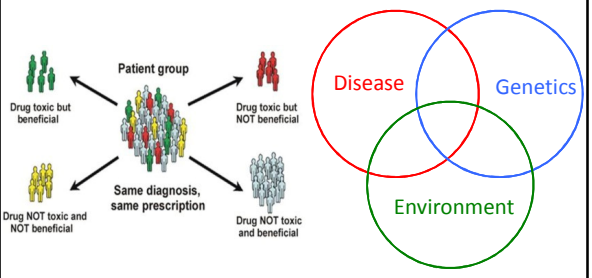
Imperfection of Drug Therapy



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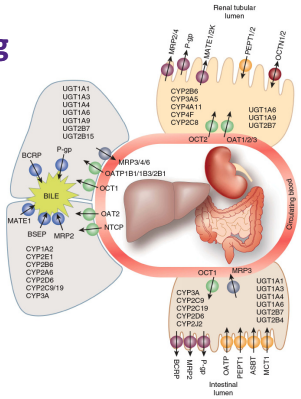
Factors Mediating Drug Disposition

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**



Yeung et al. *Kidney International* (2014)

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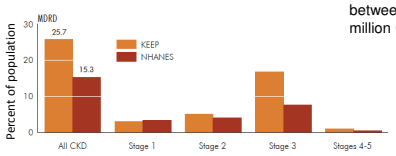
Chronic Kidney Disease (CKD)

Stage	Description	GFR (ml/min/1.72m²)
1	Kidney damage with normal or ↑GFR	≥ 90
2	Kidney damage with mild ↓GFR	60–89
3	Moderate ↓GFR	30–59
4	Severe ↓GFR	15–29
5	Kidney failure	<15 or anuric

- Characterized by a progressive decline in renal function over time.
- Major causes of CKD include diabetes and renal vascular disease (including high blood pressure)
- CKD is estimated to affect between 1.9 million and 2.3 million Canadians



Am J Kidney Dis. 2011;57(3)(suppl 2):S32-S56

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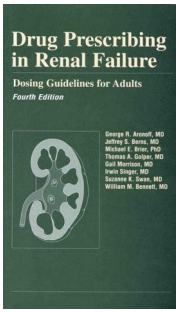
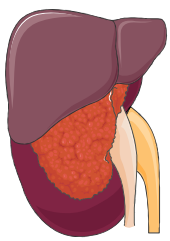
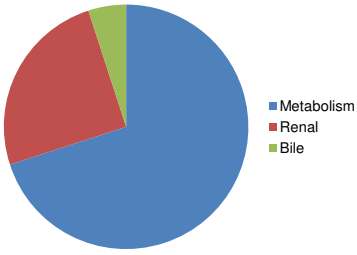
Drugs and CKD

- Patients with CKD take 7-12 medications concurrently to control a variety of co-morbidities.
- These patients have an increased incidence of adverse drug events, often due to increased blood drug concentrations.
- Many drugs are excreted by the kidney so GFR adjusted dosing in patients with CKD is common.



Drug Elimination

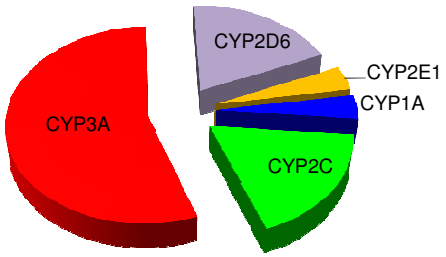




Does CKD impact hepatic drug metabolism?

Wienkers and Heath (2005) Nat Rev Drug Discov. 4 (10) 825-33

Cytochrome P450 Mediated Drug Metabolism



Shimada et al. (1994) J. Pharmacol. Exp. Ther. 270 (1) 414-23

Nuclear Receptor and Epigenetic Changes in CYP3A and CYP2C Mediated Metabolism in CKD.

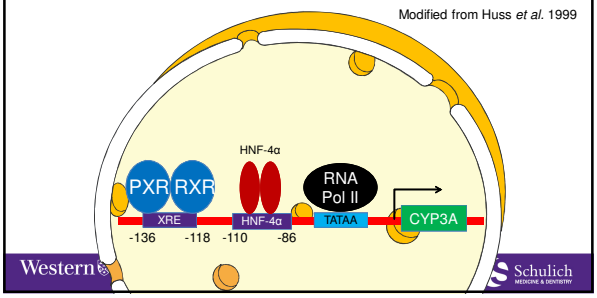
Hypothesis

Altered drug metabolism in CKD is secondary to decreased nuclear receptor binding to the CYP3A and CYP2C promoter which is associated with histone modulation.

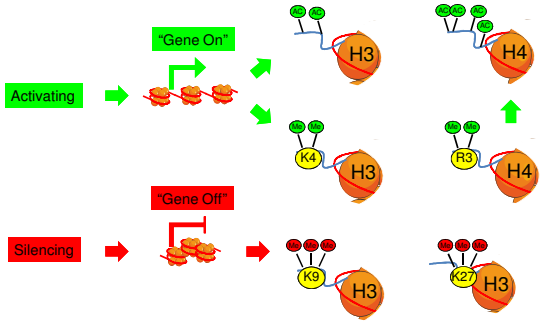
Objective

1. To determine nuclear receptor binding in CKD.
2. To investigate the epigenetic modulation of hepatic drug metabolizing enzymes in CKD.
3. To evaluate uremic toxins that may downregulate hepatic CYP3A.

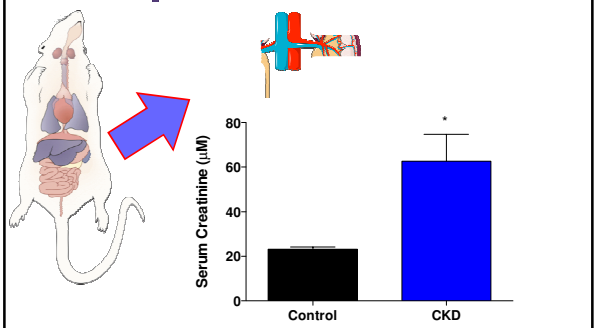
Nuclear Receptors



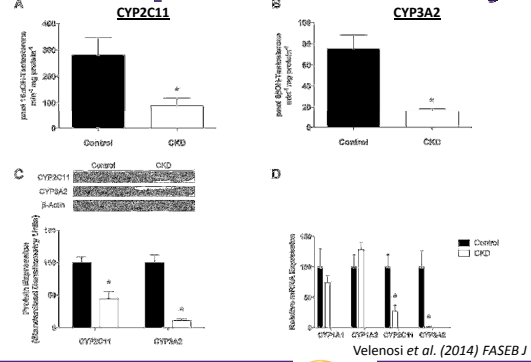
Epigenetic Modifications



Experimental Model

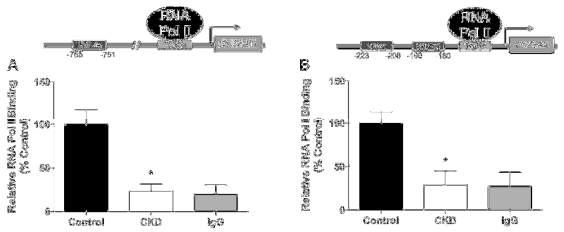


P450 Expression & Activity



Velenosi *et al.* (2014) FASEB J

CYP2C11 & CYP3A4 Transcription is Decreased In CKD



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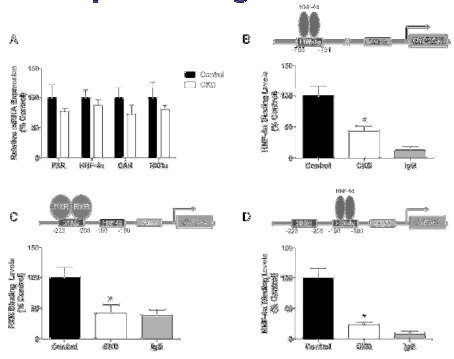
Nuclear Receptor Binding is Decreased in CKD



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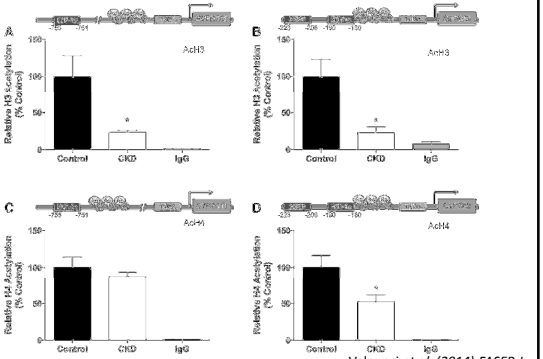
Histone Acetylation is Decreased in CKD



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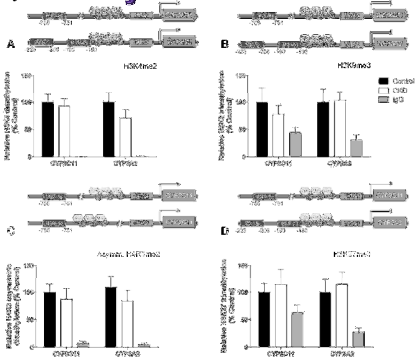
Histone Methylation is Unaltered in CKD



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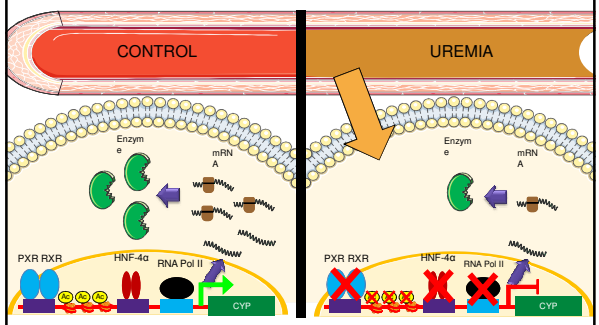
Possible Mechanism For Hepatic Drug Metabolizing Enzyme Down-regulation in CKD.

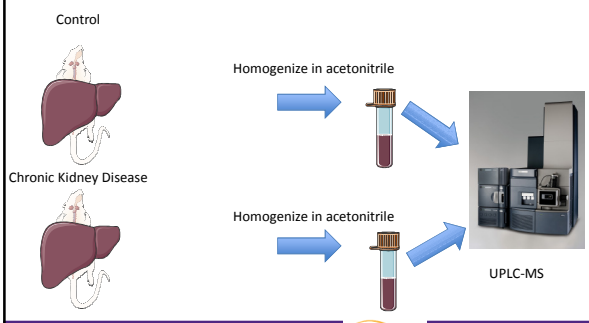


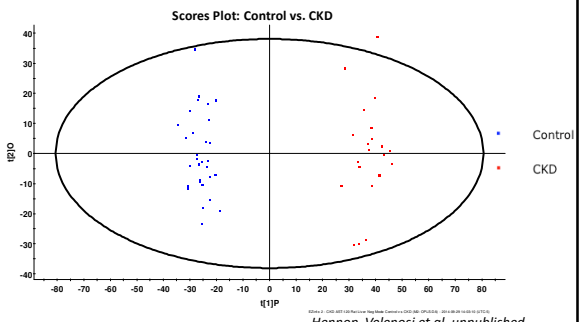
Metabolomics

- Hundreds of uremic toxins accumulate in kidney disease.
- Do any of them accumulate in the liver?
- Sensitive QTOF mass spectrometer: can quantify and identify small molecules.
- Application to drug toxicity : pharmacometabolomics

XEVO-G2-S Mass Spectrometer

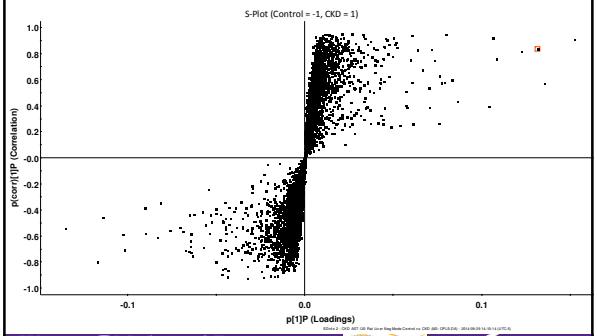
Metabolomic Investigation





Hennop, Velenosi et al. unpublished

Metabolomics of Liver Samples in CKD



Conclusions and Future Directions

CONCLUSIONS

- PXR and HNF4α binding to CYP2C11 and CYP3A2 promoters is decreased in CKD.
- Changes in histone acetylation are associated with decreased CYP2C11 and CYP3A2 expression in CKD.

FUTURE DIRECTIONS

- Metabolomic investigation to determine which uremic toxins are elevated in the liver.

Acknowledgements

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Dr. Ben Thomson

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CIHR IRSC

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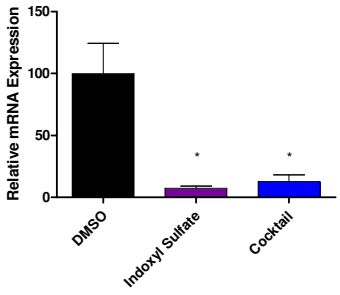
Human Hepatoma cell line (Huh7) CYP3A4 mRNA Expression

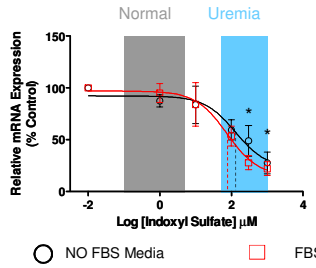


Cocktail:

- CMPF
- Creatinine
- *P*-Cresyl sulfate
- Indoxyl Sulfate
- Guanidinosuccinic acid
- Hippuric acid
- Indole-3-acetic acid
- Methylguanidine
- Urea

Velenosi *et al.* unpublished

Indoxyl Sulfate Down-Regulates Hepatic CYP3A4



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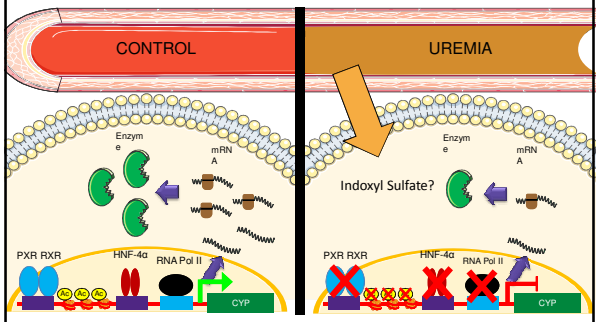

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