ANNOUNCING
Doctoral Dissertation Defense
Lashodya Dissanayake

Candidate for Doctor of Philosophy in Physiology
with a Concentration in Basic and Translational Sciences
Graduate School of Biomedical Sciences
Medical College of Wisconsin

Friday, June 24, 2022
9:00 AM CST

Zoom Meeting ID: 990 5725 0071
Passcode: JinYj7r6

Link: https://mcw-edu.zoom.us/j/99057250071?pwd=Y0FweHhzMkNFRnFnMmFWNUY1WXQ4dz09

Dissertation Committee:
Alexander Staruschenko, PhD (Advisor)
Oleg Palygin, PhD
Aron Geurts, PhD
Ashraf El-Meanawy, MD, PhD
Ilse Daehn, PhD
Graduate studies:

Graduate Human Physiology
Complement to General Human Physiology
Current Topics in Physiology
Mechanism of Cellular Signaling
Classical and Molecular Genetics
Special Problems in Physiology
Ethics & Integrity in Science
Reading and Research
Seminar
Molecules to Cells
Endocrine Regulation and Common Disease
Advanced Renal Physiology
Advanced Cardiovascular Phys
Critical Reading in Resp Phys
Physiological Genomics
Fundamental Prac Expr Grant Writing
Research Ethics Discussion Series
Integrating Pediatric Intensive Care Rounds
Boundaries of Science & Medical Practice
Doctoral Dissertation
Dissertation:
The impact of disruption of uric acid homeostasis on the kidney and blood pressure

Abstract

Uric acid (UA), the end-product of purine catabolism in humans acts as an antioxidant in circulation by scavenging free radicals. However, UA can also be considered a conditional pro-oxidant when UA is catalyzed by Xanthine Oxidase (XO), producing reactive oxygen species. UA can be produced by both XO and Xanthine Dehydrogenase (XDH) and together these enzymes are known as Xanthine Oxidoreductase (XOR). The XOR proteins are encoded by the gene XDH. The overall goal of this dissertation work was to evaluate the physiological role of the Xdh gene and elucidate the impact of both increased (hyperuricemia) and decreased (hypouricemia) UA levels in the cardiorenal syndrome continuum. The thesis is attempting to describe four key objectives: 1. investigating hypouricemia and assessing the effect of Xdh gene ablation on the kidneys using the renal phenotype in a novel rat model; 2. assessing the molecular consequences of Xdh deletion, identifying affected pathways, and proposing a molecular mechanism for pathological effects; 3. evaluating effects of Xdh gene ablation on blood pressure control and 4. evaluating the effect of hyperuricemia on salt-sensitive (SS) hypertension and examining the relationship between uricemia, uricosuria, and blood pressure in vivo.

Both hyper- and hypouricemia are associated with all-cause mortality in chronic kidney disease (CKD) patients, as well as with the risk of future kidney function decline in healthy men. Numerous studies have shown that hyperuricemia can lead to cardiovascular disease, hypertension, and CKD, and the control of UA production by XDH inhibitors can be effective in managing these conditions. Although there have been challenges in translating this knowledge to clinical practice, the mechanisms behind the pathogenesis of hyperuricemia are partially understood. Despite its clear association with poor patient outcomes, hypouricemia has been far less studied, which may be due to its lower prevalence (0.2–0.58% in the general population in some Asian countries). There are several mouse models of decreased UA production created from a knockout (KO) of the Xdh gene. These models showed severe kidney damage but had
extremely low survival probability, which is problematic for chronic physiological studies. To our knowledge, there are no hypertensive rodent models of hypouricemia. Furthermore, it has been shown that renal XOR activity increases with the increase in salt intake in Dahl SS but not in salt-resistant (SR) rats. It was also reported that long-term hyperuricemia can induce salt sensitivity in SR rats. To gain a better understanding of the role of UA in the progression of kidney injury in a SS model, we created a KO of Xdh in the Dahl SS rat background. Using this model, we tested the hypothesis that the absence of Xdh leads to kidney damage and functional decline by the accumulation of purine metabolites in the kidney and increased oxidative stress. Through the utilization of a novel genetic model, phenotyping analyses, and multi-omics analyses, we were able to uncover mechanisms of UA dysregulation leading to impairment in renal structure and function.

Uricase, the enzyme catalyzing UA further into more soluble forms is not present in humans because of a gene mutation. Due to this mutation, humans have higher levels of UA in their blood than some other mammals. This is believed to be an evolutionary advantage in regulating blood pressure and oxidative stress. Rodents possess uricase and therefore present a challenge in studying hyperuricemia in a clinically relevant way. Treating rats with oxonic acid, a uricase inhibitor has been used to overcome this issue and induce mild hyperuricemia. The role of hyperuricemia in the development of SS hypertension has not been studied. We treated Dahl SS rats with either a 4% NaCl diet (control) or a 2% oxonic acid + 4% NaCl diet (treatment) for 3 weeks. This treatment increased plasma UA level 5-fold and significantly attenuated the mean arterial pressure. These results indicated that despite having a positive correlation with hypertension in some SR models, hyperuricemia has a protective effect against SS hypertension.
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CONTACT INFORMATION:

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- USF Health Morsani College of Medicine, Taneja College of Pharmacy, and Heart Institute, 560 Channelside Dr, Tampa, FL 33602
  lashodya@usf.edu (work- current)
- lashodya@gmail.com (personal)

EDUCATION

Certificate of pre-university preparatory education
  August 2011
  Pre-medical
  Voronezh State University, Russia

Doctor of Medicine
  June 2017
  General practitioner
  Kursk State Medical University (KSMU), Russia

Doctor of Philosophy
  In progress
  In Physiology with a concentration in Clinical and Translational Sciences
  Medical College of Wisconsin (MCW), WI, USA

PUBLICATIONS


PATENTS


ABSTRACTS/PRESENTATIONS AT NATIONAL AND INTERNATIONAL CONFERENCES

Abstract oral presentation at the Hypertension Scientific Sessions (by the American Heart Association) in New Orleans, Louisiana (2019): “The Role of Xanthine Dehydrogenase (XDH) and Uric Acid (UA) in Renal Damage” at the “Mechanisms in Chronic Kidney Disease and Fibrosis” session.

Abstract poster presentation at the Experimental Biology (EB) (by the American Physiological Society/APS) – (Selected but canceled due to the Covid-19 pandemic) (2020): “The Role of XDH and UA in Renal Damage”.

Abstract oral presentation at the EB (by APS) - Virtual (2021): “A Potential Regulatory Role of XDH in the Kidney Development and Damage” in the Renal Section Young Investigator Award Featured Topic session.

Abstract poster presentation at the Kidney Week (by the American Society of Nephrology) – Virtual (2021): “Kidney Function and Renin-Angiotensin-Aldosterone System in Hypouricemia”.


Abstract poster presentation and invited oral presentation at the EB (by APS) (2022): “Therapeutic effects of L-lysine in Dahl SS rats, a Model of Salt-Induced Hypertension”


RESEARCH EXPERIENCE

Medical student researcher in the Department of General Surgery at the KSMU, Russia (2013)
Research Assistant in the Genetics research laboratory at the Kursk State University, Russia (2015-2017)

Research Assistant in the Department of Physiology at the MCW (Aug 2017-Aug 2021: in-person; Sep 2021-present: remote)

Volunteer researcher in the Department of Molecular Pharmacology & Physiology at the USF (Sep 2021-present)

SCHOLARSHIPS AND HONORS

Scholarship (full tuition remission and stipend through pre-medical undergraduate education and medical school) from the Ministry of Education and science of the Russian federation (2010-2017)

Titled “Pride of the Faculty” by the Dean of the Faculty of International students of the KSMU (2017)

Full tuition scholarship from the Graduate School of Biomedical Sciences at the MCW to complete a Ph.D. (2017- present)

Advancement to Ph.D. candidacy with above-average scoring in qualifying exam (2019)

Acceptance into the Basic and translational sciences Ph.D. program at the MCW (2019)

Recognition for being among the top 10 scored abstracts at the APS Renal Section Predoctoral Excellence in Research Award (2020)

Finalist (top 5) at the APS Renal Section Predoctoral Excellence in Research Award (2021)

Finalist (top 5) at the APS Renal Section Predoctoral Excellence in Research Award (2022)

TEACHING/MENTORING EXPERIENCE

Judge at the Milwaukee Public School STEM fair engineering design category (2018)

Judge at the University School of Milwaukee Regional Science and Engineering fair (2020, 2021)

Mentoring for the Summer Program for Undergraduate Research (SPUR) – MCW physiology department (2021)

Teaching assistant for the M1 Medical Physiology course – MCW physiology department (2021)

Basic science preceptor for the clinical-based discussions, M1 Medical Physiology course – MCW physiology department (2021)
OTHER EXPERIENCE

Interpreter (English-Russian-Sinhala) for the Ceylon Tea Board and the Embassy of Sri Lanka for Russia, Moscow (2015-2017)

LANGUAGES

Sinhala: Native proficiency

English: Full professional proficiency

Russian: Professional working proficiency

REFERENCES

Available upon request.