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GRADUATE SCHOOL

Doctoral Dissertation Defense Announcement

“Cardiometabolic Consequences of Early-Life Sodium Depletion”

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Andrew Norris, MD PhD

Date: Wednesday April 10th, 2024

Time: 1:00 PM (CST)

Defense Location: Bolger Auditorium

Zoom: Meeting ID: 974 3047 2990 Passcode: b5s8E1pB

https://mcw-edu.zoom.us/j/97430472990?pwd=S05ETGVUTnBtNk54dFBteXl1VVBkQT09

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Foundations in Biomedical Sciences II

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Dissertation Abstract

“Cardiometabolic Consequences of Early-Life Sodium Depletion”

Prematurely born infants face an enhanced risk for chronic diseases later in life, including hypertension, metabolic syndrome, and diabetes. This risk appears to be exacerbated in preterm infants who also experienced postnatal growth failure, which continues to be prevalent despite advancing and aggressive nutritional practices in this population. Sodium balance is often dysregulated in the preterm neonate and is crucial to achieve optimal somatic growth. However, the role this sodium depletion may play in long-term phenotypes remains unknown. The purpose of this project was to establish a working model of “early-life” sodium deprivation and investigate any associated long-term cardiometabolic phenotypes that may arise from adverse sodium availability in early life.

In the first study, mice were given either a low (0.04% Na) or normal/high (0.30% Na) diet from week 3 to week 18 of age. Mice given the low sodium diet displayed delays in somatic growth, as well as an increase in basal metabolic rate. In a follow up study, mice were given either 0.04% Na or 0.30% Na diet between week 3-6 of age and then returned to a standard 0.15% Na diet, to mimic an “early-life” sodium depletion. Previously Na restricted mice displayed programmed changes in feeding behaviors, reduced food intake, increased water intake, and exaggerated energy expenditure despite normal body mass and composition. Administration of hexamethonium, a ganglionic blocker, ameliorated the increase in basal metabolic rate in the previously Na restricted mice. This data indicates that early-life Na restriction is sufficient to cause programmed changes in ingestive behaviors, autonomic nervous system function, and energy expenditure that persist into adulthood.

Next, mice were again given either 0.04% Na or 0.30% Na diet between week 3-6 of age and then returned to a standard 0.15% Na diet, and then were implanted with radio telemeters to assess blood pressure and heart rate, amongst other endpoints. Early-life sodium restriction conferred no effects on blood pressure or heart rate at baseline, however, following a switch onto a high sodium diet (1% Na) as a “second-hit”, mice previously deprived of sodium had an exaggerated increase in both heart rate and systolic blood pressure in response to the high sodium diet compared to control mice. Administration of losartan ameliorated this increase in BP and HR so that both groups were indistinguishable, implicating a renin angiotensin aldosterone system dependent mechanism.

Together, these studies show that early-life sodium depletion is sufficient to program long-term changes in cardiometabolic homeostasis. This may offer mechanistic insight into a preterm neonate’s increased risk of cardiometabolic disease later in life and provide rationale for enhanced sodium monitoring in the postnatal period.

Curriculum Vitae
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Education

August 2020-Present — **Medical College of Wisconsin**
PhD Candidate, Department of Physiology
Mentors: Jeffrey Segar, MD & Justin Grobe, PhD

September 2014- December 2018 — **University of Wisconsin- Green Bay**
B.S., Human Biology, Psychology

Grant Funding

NIH T32 HL007852

Presentations

Low Sodium Supply in Early Life Causes Growth Restriction and Programs Long-Term Changes in Energy Homeostasis (*MCW Cardiovascular Center Retreat, Milwaukee WI, December 2021)*

Low Sodium Supply in Early Life Causes Growth Restriction and Programs Long-Term Changes in Energy Homeostasis *(Experimental Biology, Philadelphia PA, April 2022)*

Early Life Sodium Restriction Programs Long-Term Changes in Energy Flux and Autonomic Activity *(Hypertension Scientific Sessions, San Diego CA, September 2022)*

Long-Term Cardiometabolic and Autonomic Programming due to Early Life Sodium Depletion. *(Upper Midwest Chapter of the Society for Neuroscience Annual Conference, Green Bay WI, April 2023)*

Early Life Sodium Restriction and Programming of Autonomic and Cardiometabolic Phenotypes *(Upper Midwest Chapter of the SFN & MidBrains Combined Conference, Green Bay WI, October 2023)*

Effects of Early-Life Sodium Depletion on Growth and Energy Flux. *(UWGB Human Biology Seminar Series, Green Bay WI, October 2023)*

Publications

Ziegler, A. A., Grobe, C. C., Reho, J. J., Jensen, E. S., Thulin, J. D., Segar, J. L., & Grobe, J. L. (2022). Short-term Housing in Metabolic Caging on Measures of Energy and Fluid Balance in Male C57BL/6J Mice (*Mus musculus*). *Journal of the American Association for Laboratory Animal Science : JAALAS*, *61*(2), 132–139. https://doi.org/10.30802/AALAS-JAALAS-21-000087

Araya, B.R., **Ziegler A.A.,** Grobe, C.C., Grobe, J.L., & J.L. Segar. (2023) Sodium and Growth in Preterm Infants: A Review. *Newborn (Clarksville, Md.), 2*(2), 142-147. https://doi.org/10.5005/jp-journals-11002-0060

Grobe, C., Reho, J., Brown-Williams, D., **Ziegler, A.,** Mathieu, N., Lawton, S., Fekete, E., Brozoski, D., Wackman, K., Burnett, C., Nakagawa, P., Sigmund, C., Segar, J., & J. Grobe. (2023) Cardiometabolic Effects of DOCA-Salt in Mice Depend on Ambient Temperature.

Hypertension (Dallas, Tex. : 1979), 80(9), 1871-1880. https://doi.org/10.1161/HYPERTENSIONAHA.122.

Ziegler, A. A., Lawton, S. B. R., Grobe, C. C., Reho, J. J., Freudinger, B. P., Burnett, C. M. L., Nakagawa, P., Grobe, J. L., & Segar, J. L. (2023). Early-life sodium deprivation programs long-term changes in ingestive behaviors and energy expenditure in C57BL/6J mice. *American journal of physiology. Regulatory, integrative and comparative physiology*, 10.1152/ajpregu.00137.2023. Advance online publication. https://doi.org/10.1152/ajpregu.00137.2023