

Jagnoor K. Benipal

Medical

Louisiana State University Health Sciences Center, New Orleans, LA

Mentor: Eric Lazartigues, PhD, FAPS, FAHA

LSUHSC, Director of the Cardiovascular Center of Excellence, Professor of Pharmacology & Neuroscience; Southeast Louisiana Veterans Health Care Systems

“Chronic high salt diets contribute to neurogenic hypertension by increasing B₁R expression and B₁R-mediated ACE2 internalization and degradation”

The Centers for Disease Control and Prevention estimates that hypertension affects nearly 50% of Americans¹. Previous studies have shown that chronically elevated dietary salt intake contributes to developing neurogenic hypertension². Additionally, increased expression of the bradykinin B₁ receptor (B₁R) in neurons in the hypothalamic paraventricular nucleus (PVN) is seen in neurogenic hypertension which leads to neuroinflammation and oxidative stress³. Angiotensin-converting enzyme 2 (ACE2) is a key enzyme in the renin-angiotensin system (RAS) pathway that mitigates the vasoconstrictive effects of Angiotensin (Ang) II by cleaving it to Ang-(1-7)⁴. We previously observed that the binding of Ang-II to an Ang-II type 1 receptor (AT1R) leads to ACE2 ubiquitination and degradation⁵ by the ubiquitin ligase NEDD4-2⁶ and subsequent attenuation of its protective effects against hypertension. We are investigating the impact of a high salt-diet and how it mediates the increased expression of B₁R in the PVN and ACE2 internalization and degradation by NEDD4-2, thus contributing to the development of neurogenic hypertension. The first cohort was used to see if we could successfully induce hypertension in mice. Radiotelemetry probes were implanted into C57BL6/J male and female mice. After one week of recovery, baseline blood pressure was measured over a 24-hour period. A subset of both male and female mice were implanted with Deoxycorticosterone Acetate (DOCA) pellets and given 0.9% saline water for 4 weeks to establish hypertension. Blood pressure of all mice was recorded weekly for 24 hours. Average mean arterial pressure (MAP) was calculated for the active and resting phases of the circadian cycle by averaging MAP from 9:00 PM to 5:00 AM and 9:00 AM to 5:00 PM, respectively. By week 4, the average resting phase MAP in males and females increased by 24.13 ± 5.35 mmHg and 26.55 ± 2.04 mmHg, respectively (males: n = 6; females: n = 5), when compared to their baseline values. Additionally, the average active phase MAP in these males and females increased by 28.29 ± 6.56 mmHg and 31.65 ± 2.00 mmHg, respectively. We did not observe sex differences with this protocol. Our data show that salt-sensitive hypertension was successfully achieved in our DOCA-salt pellet protocol and giving these mice saline water. Further study is warranted to investigate the interaction of B₁R with the RAS and the role of ubiquitin proteins in ACE2 internalization.

¹ *Hypertension Prevalence in the U.S. | Million Hearts®*. (2021, March 22). Centers for Disease Control and Prevention. Retrieved July 19, 2022, from <https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html>

² Gomes, P.M., Sá, R.W.M., Aguiar, G.L *et al.* (2017). Chronic high-sodium diet intake after weaning lead to neurogenic hypertension in adult Wistar rats. *Scientific Reports*, 7(1). <https://doi.org/10.1038/s41598-017-05984-9>

³ Parekh, R.U., Robidoux, J., & Sriramula, S. (2019). Kinin B1 Receptor Blockade Prevents Angiotensin II-induced Neuroinflammation and Oxidative Stress in Primary Hypothalamic Neurons. *Cellular and Molecular Neurobiology*, 40(5), 845-857. <https://doi.org/10.1007/s10571-019-00778-1>

⁴ Sriramula, S., Cardinale, J.P., Lazartigues, E., & Francis, J. (2011). ACE2 overexpression in the paraventricular nucleus attenuates angiotensin II-induced hypertension. *Cardiovascular Research*, 92(3), 401-408. <https://doi.org/10.1093/cvr/cvr242>

⁵ Deshotels, M.R., Xia, H., Sriramula, S. Lazartigues, E., & Filipeanu, C.M. (2014). Angiotensin II Mediates Angiotensin Converting Enzyme Type 2 Internalization and Degradation Through an Angiotensin II Type I Receptor-Dependent Mechanism. *Hypertension*, 64(6), 1368-1375. <https://doi.org/10.1161/hypertensionaha.114.03743>

⁶ Ogunlade, B., Guidry, J.J., Lazartigues, E. & Filipeanu, C. (2019). ACE2 Internalization and Degradation is Controlled by Ubiquitin Ligase NEDD4. *The FASEB Journal*, 33(S1). https://doi.org/10.1096/fasebj.2019.33.1_supplement.719.14.