Anderson I. Happel
Undergraduate
Louisiana State University, Baton Rouge, LA

Dr. Eric Lazartigues, PhD
LSUHSC, Cardiovascular Center of Excellence

"Sex-specific Metabolic and Cognitive Differences in a Mouse Model of Alzheimer's Disease. Is Ang IV-IRAP signaling involved?"

BACKGROUND: Alzheimer's disease (AD) is an age-related neurodegenerative disorder that frequently exists with obesity and insulin resistance, comorbidities associated with accelerated cognitive decline and disease progression. Insulin-regulated aminopeptidase (IRAP/AT4R), the proposed receptor for angiotensin IV (Ang IV), regulates glucose homeostasis and neuropeptide metabolism. Emerging evidence suggests that dysregulation of IRAP/Ang IV axis is associated with cognitive impairment and may contribute to AD pathogenesis. We investigated early sex-specific metabolic and cognitive alterations in 5xFAD (Five Familial Alzheimer's Disease) mice. We also explored cortical IRAP expression in this strain to understand whether differences in this Ang IV receptor may be involved in the early development of AD.

METHODS: Five-month-old heterozygous 5xFAD male and female mice underwent baseline metabolic phenotyping, which included a glucose tolerance test (GTT) and an insulin tolerance test (ITT), to assess glucose tolerance and insulin sensitivity, respectively. Cognitive function was evaluated using the Novel Object Recognition (NOR) and Y-maze tests to assess short-term working memory and spatial memory, respectively. Brain tissue was analyzed by immunohistochemistry (IHC) and droplet digital PCR (ddPCR).

RESULTS: Female 5xFAD mice exhibited a trend toward impaired glucose tolerance (AUC: 727.0 ± 90.72 vs. 619.5 ± 28.82) and greater insulin resistance (AUC: 323.1 ± 18.88 vs. 284.5 ± 19.07) compared to males. Male 5xFAD mice showed decreased spontaneous alternation in the Y-maze test compared to females (30.43% vs. 38.40%, $p=0.0453$) but similar total arm entries (28 vs. 27.7, $p>0.05$), indicating impaired spatial memory in males despite equivalent locomotor activity. In the NOR test, however, females demonstrated worse object recognition memory as evidenced by reduced investigation time toward the novel object. This was shown by a reduced ratio of time spent investigating the novel object verses time investigating the familiar object (females: 0.48 ± 0.1; males: 1.25 ± 0.21, $p=0.013$). Additionally, ddPCR demonstrated reduced cortical IRAP mRNA expression in male 5xFAD mice compared to wild-type controls (12,378 vs. 19,062 copies, $p=0.008$). Consistent with these findings, IHC showed reduced cortical IRAP protein expression in male 5xFAD mice compared to wild-type controls as well as increased microglial activation, consistent with enhanced brain inflammation.

CONCLUSIONS: Our findings show distinct metabolic and cognitive differences between male and female 5xFAD mice. Reduced cortical IRAP expression and increased microglial activation in 5xFAD mice suggests that early dysregulation of IRAP signaling may be mechanistic in the neuroinflammatory and cognitive alterations observed in this strain. These findings highlight distinct metabolic and neuropathological trajectories between sexes and support IRAP as a potential therapeutic pathway in AD. Future studies will investigate whether differences in sex-specific cortical IRAP expression exist.