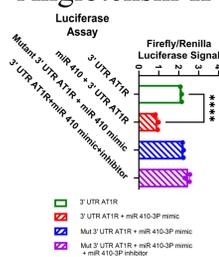


Brain miR-410-3p Expression Sex-dependently Reduces Angiotensin-II-induced Hypertension

Hope Bernier, Ayushi Patel, Vahideh Tarhriz, Huijing Xia, Eric Lazartigues.
Cardiovascular Center of Excellence, Louisiana State University Health Sciences Center - New Orleans LA

Introduction

Cardiometabolic diseases (CMD) are associated with changes in hypothalamic micro-RNA (miRNA) regulating components of the renin-angiotensin system (RAS). We recently validated miR-410-3p as a miRNA binding to the 3' untranslated region (UTR) of the Angiotensin-II type 1 receptor (AT₁R), post-transcriptionally decreasing its expression, and observed that miR-410-3p is downregulated in the hypothalamus of CMD mice.



We hypothesize that overexpression of miR-410-3p in the hypothalamus of a CMD mouse model would blunt the high blood pressure (BP) and metabolic phenotype. This study investigates the role of miR-410-3p as a potential therapeutic agent.

Timeline of Experiment

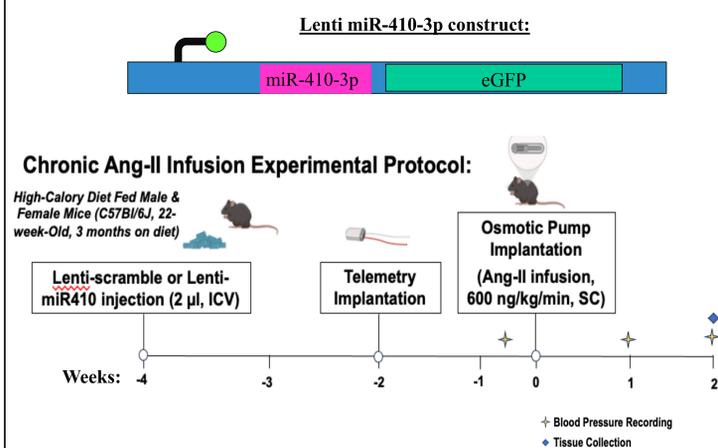


Figure 1. Two microliters of lentivirus were injected in the lateral ventricle (icv) of each mouse fed a high-fat diet for 3 months. Two weeks later, telemetry probes were implanted into the mouse' left carotid followed by subcutaneous implantation of osmotic pumps filed with Angiotensin-II, two weeks after this. Blood pressure was recorded for 24 hours at baseline and weekly for 2 more weeks.

Brain GFP Expression Post ICV Injection

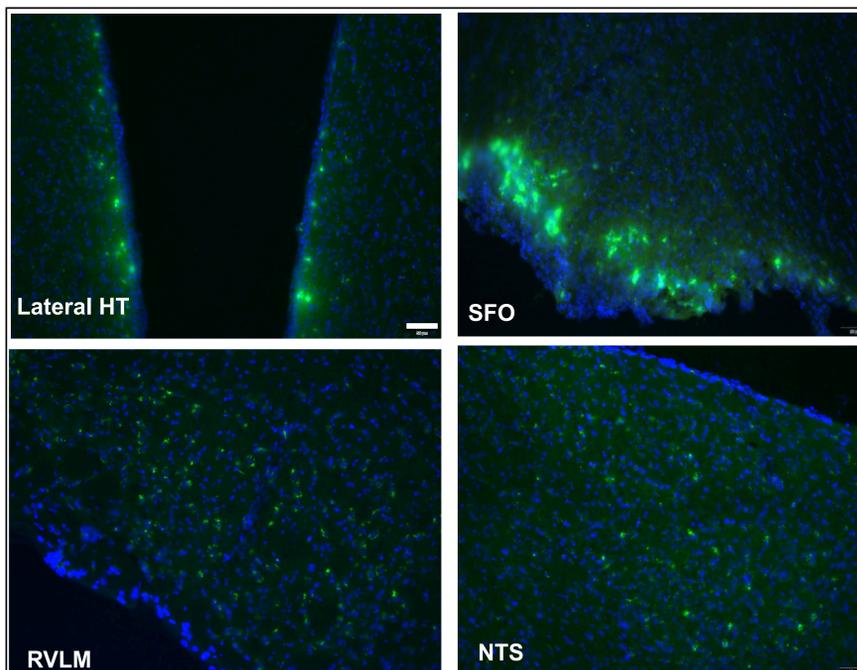


Figure 2. MiR-410-3p Expression in the Brain Three Weeks Post-ICV Injection. Three weeks post-lenti-miR-410-3p-GFP ICV injection, GFP fluorescence was observed in the paraventricular nucleus (PVN), subfornical organ (SFO), rostro ventrolateral medulla (RVLM), and nucleus tractus solitarius (NTS). This demonstrates the expression of miR-410-3p in brain regions involved in blood pressure control. Scale bar: 50 µm.

miR-410-3p Sex-Dependently Alter Glucose Tolerance

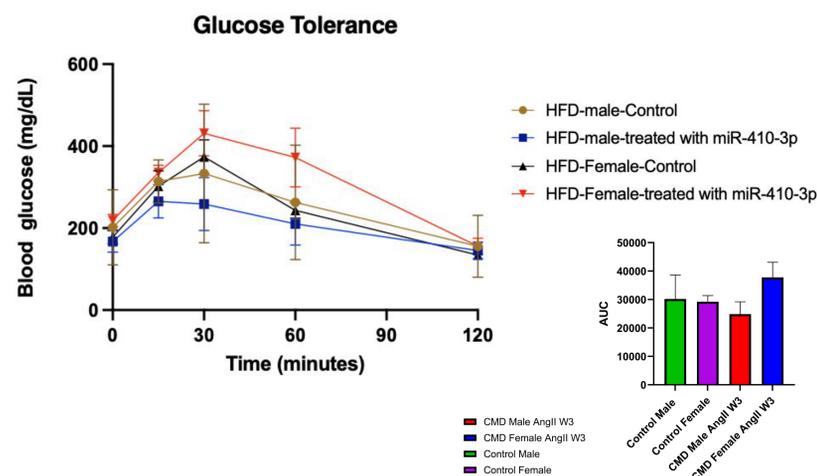


Figure 3. miR-410-3p Females were Less Tolerant to Glucose. GTT showed that females treated with miR-410-3p exhibited a trend towards reduced glucose tolerance compared to control females while treated males seem to show improved glucose tolerance versus control males.

miR-410-3p Sex-Dependently Inhibit Chronic Ang-II Infusion-Induced Increases in BP

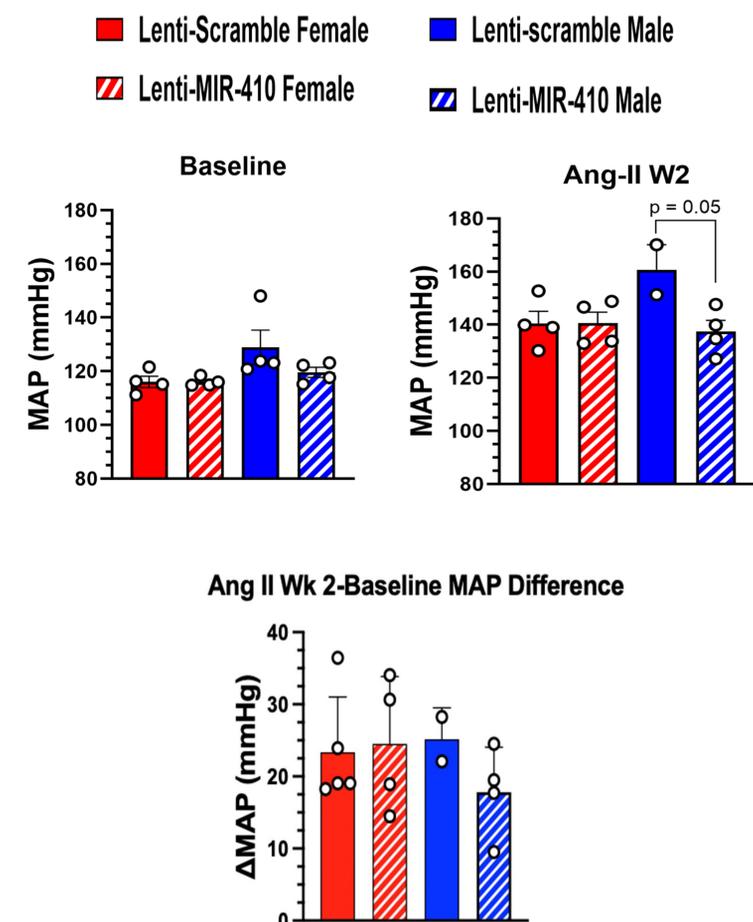


Figure 4. Effect of Lenti-miR-410-3p on Mean Arterial Pressure (MAP) in Response to Chronic Ang-II Infusion in Male and Female Mice. (A) Baseline MAP was similar between male scramble and lenti-miR-410 groups and between female scramble and lenti-miR-410 groups. (B) After 2 weeks (W2) of Ang-II infusion, MAP increased in both sexes treated with the scramble control virus. Interestingly, lenti-miR-410-3p expression blunted this increase in males (137.3 ± 9.4 vs. 160.7 ± 4.3 mmHg, $P=0.05$), but not in females (140.4 ± 4.6 vs. 140.5 ± 4.2 mmHg). (C) Δ MAP was similar between both female groups, however there is a notable decrease in Δ MAP in the male lenti-miR-410-3p group compared to the male scramble control group.

Conclusion

miR-410-3p blunted the hypertensive effects of Angiotensin II in a sex dependent manner. There is potential for therapeutic use of miR-410-3p, but the experiment will need to be repeated with a higher titer lentivirus.