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

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 type I receptor (AT_1R), 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. Using a bioinformatic database (TargetScan) our analysis identified homologous miRNA sequences that directly target the AT_1R in both mice and humans. In vitro, cultures of brain endothelial cells (bend3) confirmed that miR-410-3p mimics reduced AT_1R expression. Accordingly, a commercial lentivirus containing miR-410-3p was designed to be injected intracerebroventricularly (icv) into a CMD mouse model. The virus contained a green fluorescent protein (GFP) tag to detect expression in brain tissue. Four-week-old mice (20 males and 20 females) were placed on a high fat diet (60% kcal from fat) for two months prior to icv injection (2 µl) of Lenti-miR-410-3p virus or Lenti-control virus. Three weeks after injection, telemetry probes were implanted in the carotid artery of the mice for continuous BP monitoring. Twenty-four-hour recordings of BP were obtained weekly before and during four weeks after implantation of osmotic pumps containing Ang-II (600 ng/kg/min). Glucose tolerance tests (GTT) were also performed before and after completion of Ang-II infusion. Mice were euthanized and brains were sectioned for microscopic imaging. GFP fluorescence was observed throughout the brain, including the paraventricular nucleus (PVN), nucleus tractus solitarius (NTS) and rostral ventrolateral medulla (RVLM). Two weeks after Ang-II infusion, BP was increased in both control males and females (165±9 and 143±4 mmHg, respectively, $P<0.05$). Male mice treated with Lenti-miR-410-3p had a blunted BP (144±4 vs. 166±10mmHg, $P < 0.05$), while the treatment had no effect on BP in females (145±3 vs. 144±4 mmHg, $P=0.91$). These findings are consistent with previous data showing that the hypothalamus in male mice has greater AT_1R expression. Additionally, GTT showed that females treated with Lenti-miR-410-3p were less tolerant to glucose than control females (AUC: 37,252±2,839 vs. 27,296±2484, $P<0.05$), while treatment had no impact in male mice (AUC: 38,845±3809 vs 32,728±2,478, $P=0.20$). This could suggest that while targeting AT_1R in the hypothalamus might be beneficial in reducing BP, targeting other miR-410-3p targets (e.g. MDM2) might not be so desirable. In conclusion, miR-410-3p blunts the hypertensive effects of Ang-II, with greater effects in males than females, supporting a therapeutic role for miR-410-3p for the treatment of CMD.