Gestational Intermittent Hypoxia Impairs AT2R-Mediated Cardiovascular Protection in Female Offspring on a High-Fat, High-Sucrose Diet

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Gestational intermittent hypoxia (GIH), a hallmark of maternal obstructive sleep apnea, exhibits sex-specific consequences, leading to hypertension and endothelial dysfunction in adult male offspring but not in females. This study investigated whether GIH-exposed female offspring, a "protected" group against the hypertensive effects of maternal GIH exposure, exhibit increased susceptibility to hypertension and cardiovascular dysfunction when fed a high-fat, high-sucrose (HFHS) diet, and whether this effect could be reversed by pharmacological intervention activating the angiotensin II type 2 receptor (AT2R). Female offspring of GIH-exposed (10.5% O2, 8 h/day, E10-21) and control dams were assigned either an HFHS diet or a control diet from 12 weeks of age. Blood pressure was monitored weekly using the CODA tail-cuff system. At 28 weeks of age, the control and GIH offspring with and without HFHS diet received a systemic infusion of either CGP42112 (AT2R agonist) or saline for 2 weeks through mini osmotic pump, and blood pressure was recorded. At 30 weeks, the animals were euthanized, and mesenteric arteries were collected for assessment of vascular reactivity and protein analysis. Plasma was collected for measurement of bradykinin levels using ELISA. The HFHS diet induced similar increases in body weight gain and blood pressure in both control and GIH female offspring. Vascular contractile responses were unaltered, but endothelial-dependent vascular relaxation was impaired, accompanied by decreased AT2R and eNOS expression and reduced plasma bradykinin levels in both control and GIH female offspring on the HFHS diet. CGP42112 administration effectively mitigated HFHS-induced hypertension and endothelial dysfunction only in control female offspring, accompanied by restoration of AT2R, eNOS, and bradykinin levels, but not in GIH counterparts. These findings suggest that GIH induces endothelial dysfunction and AT2R insensitivity in female offspring exposed to an HFHS diet.