Aberrant Estrogen Metabolism in Preeclampsia may Cause Dysregulation of Angiogenesis-mediated Uterine Blood Flow via a Novel Uterine Endothelial Adrenergic System

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During pregnancy uterine angiogenesis mediates rises in uterine blood flow and thus nutrient delivery to growing fetuses. Estradiol-17β (E2) and several metabolites that are synthesized by cytochrome P450s (cytoP450s) and catechol-O-methyltransferase (COMT) are elevated during gestation. Alterations in estrogens and its metabolites during normal and preeclamptic pregnancies therefore may have significant systemic cardiovascular and local uterine hemodynamic functional roles. We observe that preeclampsia lowers estrone, estradiol-17β, and a number of metabolites. Pregnant ovine Uterine Artery Endothelial Cell (P-UAEC) model express cytoP450s, COMT, estrogen receptor (ER)α, and ERβ as well as adrenergic receptor (AR)α2, ARβ2 and ARβ3, but not ARα1 and ARβ1. E2β and a number of metabolites concentration-dependently stimulated proliferation of P-UAECs. Cell proliferative responses to E2β were solely mediated by ERβ (not ERα), whereas responses to all metabolites of E2β were neither ERα nor ERβ mediated. Because catecholestradiols and catecholamines exhibit structural similarities and have high affinity for ARα and ARβ, we hypothesized the existence of a novel uterine endothelial adrenergic system and investigated if the endothelial ARα or ARβ mediate catecholamine and catecholestradiols stimulated proliferation of P-UAECs. Norepinephrine and epinephrine-induced P-UAEC proliferation responses were suppressed by propranolol (ARβ blocker), but not phentolamine (ARα blocker). Catecholestradiol-induced P-UAECs proliferation was also inhibited by propranolol, but not phentolamine. AR β2 and ARβ3 antagonists abrogated the mitogenic effects of select estradiol metabolites. Therefore the P-UAEC proliferative responses of both catecholamines and catecholestradiols were not ER mediated, but rather via β2-ARs and β3-ARs. Aberrant synthesis and metabolism of estrogens and estrogen metabolites in preeclampsia provides direct clinical insight for these steroids in pregnancy and highlight critical links to reduced uterine perfusion in hypertensive gestations. We report a novel uterine endothelial adrenergic sympathomimetic system and demonstrate important functional roles for E2β, and its CYP450- and COMT-derived metabolites in uterine angiogenesis regulation during pregnancy that may be dysfunctional in preeclampsia. There is important signaling intermediate convergence of the endothelial ER and AR systems in regulating endothelial proliferation, thus providing a distinct evolutionary advantage for positively modulating uterine perfusion during stressful pregnancies.