Ovariectomy Promotes Angiotensin II-induced Renal Dysfunction and Vasopressin Excretion via 12/15-Lipoxygenase

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Abstract ID 51393 Poster Board 312

Hypertension is a major risk factor that contributes to kidney injury in women. While the female sex hormone 17β-estradiol (E2) has been shown to be cardioprotective in experimental models of cardiovascular diseases, E2 replacement therapy in postmenopausal women has been controversial. We have shown previously that ovariectomy (used as a tool to deplete endogenous E2) augments angiotensin (Ang) II-induced increase in blood pressure and plasma level of 12(S)-hydroxyeicosatetraenoic acid (HETE), a major arachidonic acid metabolite produced by 12/15-lipoxygenase (ALOX15). ALOX15 and its arachidonic acid-derived metabolite 12(S)-HETE is implicated in cardiovascular and renal diseases. This study was conducted to investigate the contribution of ALOX15 to Ang II-induced renal dysfunction in intact and ovariectomized (OVX) female mice. Ang II (700 ng/kg/min) infused subcutaneously by osmotic pumps for 2 weeks caused a marked increase in water intake (mL; 10.5±0.64 vs 5.0±0.40), and renal dysfunction as evidenced by increased urine output (mL; 5.06±0.43 vs 1.56±0.15), decreased urine osmolality (mOsm/Kg; 1.27±0.04 vs 2.10±0.06) and increased urinary excretion of vasopressin prosegment copeptin (pg/mL; 149.53±3.47 vs 122.13±1.00) measured by ELISA in OVX but not intact (with ovaries intact) wild type (WT) mice (n=4/group, p<0.05). These effects of Ang II were attenuated in intact and OVX Alox15 knockout (ALOX15KO) female mice (water intake: 4.0±0.41 and 5.25±0.47; urine output: 1.18±0.11 and 1.00±0.10; urine osmolality: 2.56±0.27 and 1.78±0.07; urinary excretion of copeptin: 122.9±0.56 and 118.0±3.76; n=4/group, p<0.05). Moreover, in OVX-WT mice with depleted plasma E2 (pg/mL; 1.00±0.26 vs 14.71±1.38; n=4, p<0.05, measured by ELISA), the effects of Ang II on renal hypertrophy expressed as total kidney/body weight ratio (mg/g; 12.19±0.55 vs 9.16±0.22; n=6, p<0.05) and reactive oxygen species production measured by increased 2-hydroxyethidium fluorescence on staining with dihydroethidium (arbitrary unit; 16.73±0.63 vs 4.33±0.09, n=4, p<0.05), were also enhanced compared to intact WT mice. These effects of Ang II were attenuated in both intact and OVX-ALOX15KO mice (plasma E2: 13.96±1.75 and 1.29±0.44, kidney/body weight: 9.48±0.18 and 10.10±0.33, reactive oxygen species: 1.55±0.07 and 1.82±0.02). These data suggest that ovariectomy or lack of 17b-estradiol promotes Ang II-induced hypertension and renal dysfunction, most likely by a mechanism dependent on ALOX15/12 (S)-HETE. Therefore, the selective inhibitors of ALOX15 or 12 (S)-HETE receptor antagonists could be useful for treating hypertension and associated pathogenesis in postmenopausal, hypoestrogenic women or females with ovarian failure. Furthermore, it has been reported that that two single-nucleotide polymorphisms in the Alox12 gene, rs9904779 and rs434473 (encoding a replacement of asparagine by serine in the protein), was associated with onset of natural menopause in a small set of white women studied. Therefore, it would be important to explore ALOX15 gene polymorphism further in a larger population of diverse groups of normal aging and pre- and postmenopausal females to determine its impact on the contribution of arachidonic acid-ALOX15 derived 12(S)-HETE in hypertension and its pathogenesis.