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## Estradiol replacement mitigated blood pressure elevation via suppression of sodium chloride cotransporter in angiotensin II-infused ovariectomized female rats

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**Objectives:** Female rats excrete more urine sodium than male rats with similar blood pressure (BP). However, it is not clear whether the sex difference in pressure natriuresis is conserved in menopausal rats. We assessed whether the natriuretic response and renal sodium transporter activity in ovariectomized female rats infused with angiotensin II (ANGII) could be affected by estrogen supplementation.

**Methods:** Six-week-old female Sprague-Dawley rats (n=30) were ovariectomized (OVX, n =20) or sham-operated (n=10) (-4 weeks, -4W). After 2 weeks, subcutaneous estradiol was administered to half of the OVX rats (n=10) for 4 weeks (-2W~2W). ANGII was infused via the osmotic minipump in 60% of the rats for 2 weeks (0W~2W). Six groups (female saline: FS, female ANGII: FA, OVX saline: OS, OVX ANGII: OA, OVX estradiol saline: OES, OVX estradiol ANGII: OEA) were sacrificed after 2 weeks of the ANGII infusion (2W). We also analyzed human data from the Korean Genome and Epidemiology Study (KoGES).

**Results:** ANGII-induced BP elevation was highest in the OA group, followed by the FA and OEA groups. Urine sodium tended to increase after ANGII infusion in FA and OEA but decreased in OA. Western blot results showed that cortical phosphorylated sodium chloride cotransporter (pNCC) tended to be augmented by ANGII treatment in FA and OA, but mitigated in OEA. Cortical ANGII type 2 receptor (AT<sub>2</sub>R) expression was significantly higher in estradiol-treated OVX rats than in OVX rats, irrespective of ANGII infusion. Similarly, the enhanced pNCC in ANGII-treated distal convoluted tubular cells was reversed by estradiol treatment. In KoGES data, urine sodium was significantly lower in postmenopausal women than in premenopausal women, despite the higher BP.

**Conclusions:** Estradiol reversed BP elevation and augmented the natriuretic response in ANGII-infused OVX rats and distal tubular cells via suppression of pNCC and increase of AT<sub>2</sub>R.

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