Deletion of Endothelial Estrogen Receptor Alpha Reduces Arterial Stiffness in Angiotensin II infused-Female Mice

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ABSTRACT

Background: Vascular stiffness is a naturally occurring phenomenon associated with aging, but conditions such as obesity and type 2 diabetes accelerate its development, particularly in women. The presence of vascular stiffness increases significantly the risk of cardiovascular disease (CVD). Under physiological conditions, estrogen signaling via estrogen receptor alpha (ERα) increases bioavailable nitric oxide in the endothelium and decreases stiffness. Nevertheless, large clinical trials have failed to demonstrate beneficial cardiovascular effects of estrogen therapy. Our previous work has shown that under conditions of over-nutrition, the lack of ERα ameliorates arterial stiffening in obese and insulin resistant females. Given the central role that activation of the Renin-Angiotensin-System (RAS) has in the pathogenesis of CVD, in the present study we examine the effect of an Angiotensin II (Ang II) infusion in female mice lacking endothelial cell (EC).

METHODS

Animals: Mice harboring a floxed Esr1 gene were bred to mice expressing a VE-cadherin-Cre to obtain EC deleted line of Ers1 (KO). As control we utilized the doubled floxed mice.

Ang II infusion: 24 week old mice were treated with Ang II (500 ng/kg/min) via osmotic minipumps for 4 weeks (n=5 per group).

Aortic stiffness and vascular reactivity: Aortic stiffness was evaluated in vivo by ultrasound-based pulse wave velocity (PWV). Endothelial- dependent and -independent vasomotor responses were evaluated in isolated aortic rings.

Femoral artery stiffness and remodeling: Arteries were isolated and cannulated onto glass micropipettes, pressurized at 70 mmHg without flow, and warmed to 37°C in commercial myograph chambers. Vessels were then placed in Ca2+-free PSS and exposed to consecutive changes in intraluminal pressure from 5 to 120 mmHg while under passive conditions to determine the elastic properties of the artery.

Statistics: Results are presented as means ± SE analyzed by Student’s T-test, p < 0.05 was considered as significant.

RESULTS

Table 1. Characteristics at sacrifice of the different cohorts. Wild type (WT). ER ERα KO (KO). After 4 weeks of Ang II infusion there was a trend toward higher blood glucose in the KO mice. n=5 per group.

<table>
<thead>
<tr>
<th></th>
<th>WT + Ang II</th>
<th>KO + Ang II</th>
<th>p</th>
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<tbody>
<tr>
<td>Body Weight (g)</td>
<td>21.96 ± 0.23</td>
<td>22.2 ± 0.15</td>
<td>0.4</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>134.8 ± 6.33</td>
<td>158 ± 7.95</td>
<td>*0.05</td>
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<tr>
<td>Heart/tibia length</td>
<td>73.84 ± 3.02</td>
<td>70.63 ± 4.42</td>
<td>0.39</td>
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Figure 1. Deletion of ERα does not result in significant differences in arterial stiffness assessed by PWV, n=5 per group.

Figure 2. Absence of EC ERα does not result in significant differences in arterial stiffness assessed by PWV, n=5 per group.

Figure 3. Deletion of ERα does not result in significant differences in aortic endothelial dependent or independent vasodilatory responses. (A) Acetylcholine dose-response curve (B) Sodium nitroprusside (SNP) dose-response curve. n=5 per group

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CONCLUSIONS

✓ Deletion of ERα in endothelial cells in the setting of RAS activation promotes hyperglycemia.

✓ In conditions RAS activation , EC absence of ERα does not result in significant impairment in endothelial-dependent or -independent aortic dilatation.

✓ Deletion of ERα in EC decreases femoral artery stiffness (decreased modulus of elasticity) and increases compliance, which might precede the development of aortic stiffness

✓ Future studies are needed to elucidate the mechanisms underlying the relationship between estrogen signaling and vascular dysfunction