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ESTROGEN INDUCES ANGIOGENESIS GROWTH INTO SMOOTH MUSCLE CELLS OF FEMALE RABBIT BLADDER

Hypothesis / aims of study

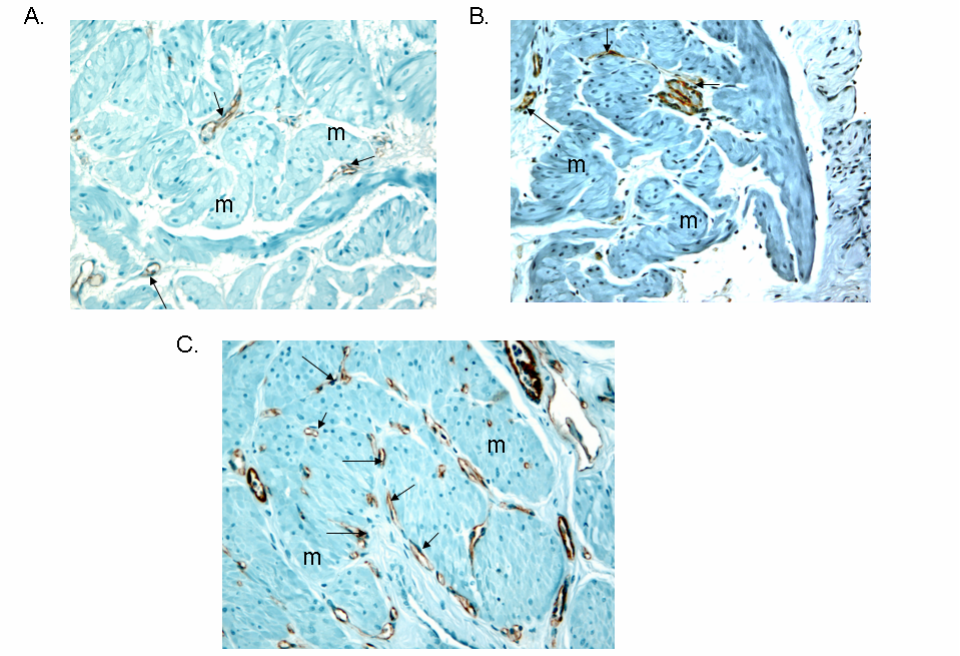
Postmenopausal bladder dysfunction has been speculated to be partly due to the influence of estrogen. Estrogen is essential for adequate blood flow in the urinary bladder and urethra. Our previous studies have demonstrated that estrogen augmentation in female rabbits induces a “functional hypertrophy” consisting of increased contractile force, increased blood flow, and increased volume-fraction of smooth muscle of the urinary bladder. It is our hypothesis that angiogenesis is promoted by estrogen augmentation, which contributes to the enhanced blood flow to supply the enlarged bladder as well as the hypertrophied smooth muscle cells. The present study is to investigate the effects of ovariectomy and estrogen augmentation on vascularity and angiogenesis.

Study design, materials and methods

24 New Zealand White female rabbits were separated into 6 groups of 4 each. Group 1 served as control, group 2 to 6 were ovariectomized, and group 2 served as the ovariectomy (Ovx) without estradiol. 2 weeks after Ovx, groups 3 to 6 were given 17-β estradiol (1 mg/kg/day) by subcutaneous implant for 1, 3, 7 and 14 days, respectively. Angiogenesis was investigated by immunohistochemical studies of smooth muscle tissue sections. Proteins were extracted and the expression of Vascular Endothelial Growth Factor (VEGF) and Hypoxia Inducible Factor (HIF-1α) were determined using western blotting. In addition, vascularity was evaluated and quantitated by CD-31 immunohistochemistry and digital image analysis.

Results

Ovx resulted in significant vascular degeneration, whereas estradiol augmentation showed significantly enhanced vascularity. Moreover, in the 14-day estradiol group, neovascularization developed within the matrices of smooth muscle bundles. Figure 1 shows representative photo-micrographs of control, Ovx, and Ovx followed by 2 weeks estrogen showing vascularity using CD-31 immunohistochemistry. In both the control and Ovx bladders, the large majority of blood vessels travel between the discrete muscle bundles (black arrows in A& B). Following estrogen supplementation, the new blood vessels are observed both within the muscle bundles and between the individual muscles cells (black arrows in C). The expression of angiogenic markers, VEGF and HIF- 1α was found to be significantly increased in Ovx groups when compared to control, the expression of which was decreased in 1 day estradiol group. Their expression was increased three fold in both the 7 day and 14 day treatment groups.
Figure 1



Interpretation of results

Ovx resulted in vascular degeneration consistent with the previous demonstration of decreased blood flow and hypoxia. Estradiol augmentation induced functional hypertrophy of female rabbit bladder and subsequent vasculogenesis correspond to the previously observed increased blood flow.

Concluding message

Estrogen induces angiogenesis growth into smooth muscle cells of the female rabbit urinary bladder. Most interesting is that many of the new blood vessels are localized within the smooth muscle matrix. This particular phenomenon may improve our understanding of angiogenesis.

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