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Clark A, Otto L, Slayden O, Brenner R
Oregon Health and Sciences University

RALOXIFENE SUPPRESSION OF VAGINAL SMOOTH MUSCLE

Aims of Study

To measure the effect of estradiol and raloxifene compared to estrogen deprivation on the vaginal smooth muscle of the Rhesus macaque.

Methods

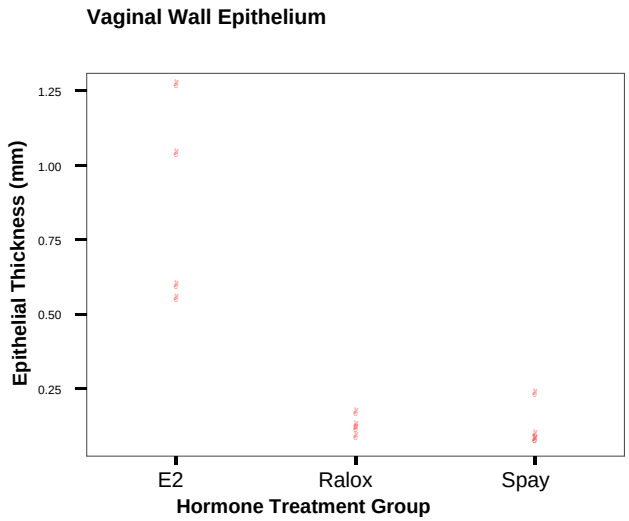
Twelve nulliparous young adult females underwent oophorectomy, and 4 animals were assigned to each of 3 treatment groups: estradiol implant (serum estradiol 33-72 picograms/dl), estrogen deprivation (spay), and daily oral raloxifene (5 mg/kg). The entire vagina was removed at necropsy, retaining its attachments to the pelvic floor muscles, the bladder, the rectum, and cervix. Full thickness histologic preparations of the anterior vaginal wall were made after carefully dissecting away the bladder and urethra. Full thickness sections of the lateral vaginal wall were made, retaining the attachment to the levator ani. Estrogen and progesterone receptor assays were performed by immuno-cytochemistry on paraffin-imbedded tissue. Photomicrographs were digitized for morphometric analysis using ImagePro software. The proportion of smooth muscle in the fibro-muscular wall was measured in paraffin-imbedded specimens stained with Masson's Trichrome, by thresh holding the red color of the smooth muscle against the blue connective tissue background.

Results

Estrogen receptors were present in the nuclei of epithelial cells, fibroblasts, and smooth muscle cells. Progesterone receptors were up-regulated by estradiol treatment, consistent with behavior in other estrogen-sensitive tissues.

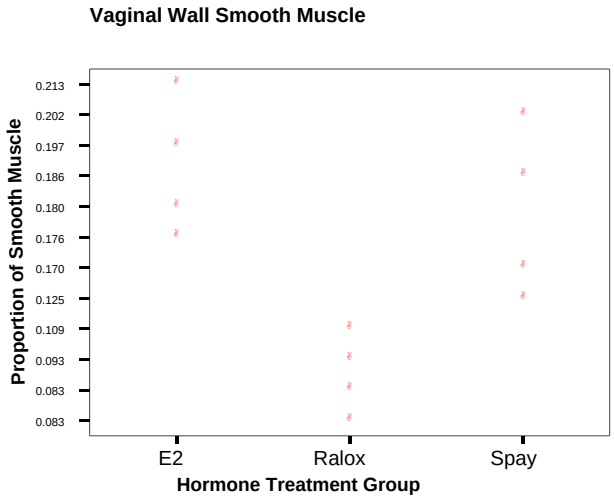
The different layers of the vaginal wall show differential sensitivity to the presence of estrogen and raloxifene. The epithelium is significantly thinner in the spayed (0.11mm∀0.07) and raloxifene treated (0.11mm ∀0.03) groups compared to the estrogen treated (0.85mm∀0.34) groups (Figure 1). However, there were no differences in overall thickness of the vaginal wall (lamina propria, fibro-muscular layer or total wall thickness) among the three treatment groups.

Figure 1



Of great interest, raloxifene suppressed the proportion of smooth muscle bundles within the fibro-muscular layer significantly below the amount found in the spayed, untreated group. For example, the proportion of smooth muscle in the fibro-muscular layer of the raloxifene group was 51% less than in the estradiol group (p=0.002), while there was no difference between the spayed and estrogen treated groups in this measurement (Figure 2).

Figure 2



Conclusions

The smooth muscle of the vagina was specifically and significantly suppressed by raloxifene treatment, below the amount seen in the absence of estrogen. The data suggest that this selective estrogen receptor modulator (SERM) has a specific inhibitory effect on one element of the vaginal fibro-muscular tube. This specific action of raloxifene should be considered when assessing the possible link between use of SERM's and the development of pelvic organ prolapse.

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