**372**

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# NEONATAL EXPOSURE TO ENVIRONMENTAL DISRUPTORS DECREASES ESTROGEN RECEPTOR-BETA AND SUPPRESSES APOPTOSIS OF THE PROSTATE AFTER PUBERTY

## Hypothesis / aims of study

Effects of environmental endocrine disruptors on the male reproductive system have received much attention, but little is known about whether these contaminants may influence prostate growth. Epithelial component of ventral prostate in beta-ERKO mice was increased(1). We previously reported that low-dosage estrogen exposure in the neonatal period increased DHT concentration and decreased estrogen receptor-beta (ERB) in ventral prostate, engendering decreased apoptosis and formation of glandular hyperplasia(2) . We examined the mechanism of prostate enlargement to estimate ERB androgen receptor (AR), DHT concentration, morphometry, and apoptosis of prostates in rats that were exposed to environmental endocrine disruptors during the neonatal period.

## Study design, materials and methods

Subjects were 32 male Wistar rats. Sixteen rats were injected with 25 µg Estradiol on days 1, 3, and 5 after birth (Estrogen group); the others served as the control group (oil injection). Each groups' rats were sacrificed on days 80, 125, 160, and 180. Their blood was collected to determine serum testosterone. Intra-prostate dihydrotestosterone (DHT) concentration was calculated by LC-MS/MS. Real time quantitative PCR measured AR and ERB mRNA of the ventral prostate. Quantitative morphometry measured their histological compositions. Immunohistochemical analysis of Proliferating Cell Nuclear Antigen (PCNA) indicated the degree of apoptosis.

## Results

The relative weight was increased significantly in only Estrogen group after 180 days. Histomorphometry showed relatively increased epithelial components of the exposure group at day 160. Malignant change was not found in any rats. The DHT concentrations of prostate were significant low in Estrogen group at 120 day, but after 160 days, those were high. At days 160 and 180, AR and ERB mRNA were low in the exposure group. Expression of PCNA at day 160 was increased significantly for rats exposed to estrogen (control: Estrogen 2.90±. 08‰: 15.0±9.2‰).

## Interpretation of results

Because epithelial component and positive rate of PCNA staing cells were increased after 160 days, ERB has the possibility to accelerate apoptosis and regulate androgen system, especially intra-prostate DHT concentration.

## Concluding message

Low-dose estrogen exposure in the neonatal period decreases ERB after puberty and suppresses apoptosis after middle age. In puberty, decreasing ERB led to glandular hyperplasia of the prostate. These processes result in differences of individual prostate components. Because neonatal time for rat is equivalent to the last fetus for human, the differences of human prostate components may be depended on the pregnant mother's eating habits.

**Table**
Comparison of each parameters between normal and neonatal estrogen exposure rats

| | Vent/BW | | Prostatic DHT | | ERB /18s | |
|---|---|---|---|---|---|---|
| Day | control | Estrogen | control | Estrogen | control | Estrogen |
| 80 | 1.27±.22* | 0.79±.27* | 8.10±.44 | 6.36±.76 | | |
| 120 | 1.64±.64 | 1.29±.61 | 9.65±1.55* | 7.40±.38* | .20±.13 | .09±.06 |
| 160 | 1.77±.70 | 1.66±.48 | 4.82±.61* | 8.49±1.24* | .40±.20* | .20±.10* |
| 180 | 1.65±.14* | 1.25±.18* | 6.30±.48 | 5.93±.35 | .92±.41* | .15±.09* |

Vent/BW; ventral prostate / body weight ratio.
Prostatic DHT: intra-prostate dihydrotestosterone
* $p < 0.05$

**References**

(1) A role for estrogen receptor-beta in the regulation of growth of the ventral prostate. Proc. Natal. Acad. Sci. USA 2001; 98:6330- 6335
(2) Neonatal estrogen exposure leads to prostatic hyperplasia by decreasing estrogen receptor-beta in the prostate and increasing prostate dihydrotestosterone concentration. J Urol.:2003; 169(4): 282