

# Developmental exposure to bisphenol A increases prostate cancer susceptibility in adult rats: epigenetic mode of action is implicated

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Similar to the testes, male accessory sex glands are also vulnerable to environmental endocrine disruptors with adverse effects in adulthood. The developing prostate gland is particularly sensitive to estrogens, and high-dose exposures during a critical developmental window results in intraepithelial prostatic neoplasia (PIN) in adult rodent models. Bisphenol A (BPA), a ubiquitous environmental contaminant leached from plastics and epoxy resins, has estrogenic activity. Although neonatal exposure to environmentally relevant doses of BPA produced no prostate pathology in the adult rat, we asked whether it would sensitize the adult prostate to estrogenic exposures. Relative estrogen levels rise in the aging male and adult estrogen exposures can be carcinogenic to the prostate gland. To test this possibility, newborn rats were exposed to a low dose of BPA (10  $\mu\text{g}/\text{kg}$  body weight) or to a low dose (0.1  $\mu\text{g}/\text{kg}$  body weight) or high dose 2.5  $\text{mg}/\text{kg}$  body weight) of estradiol (E) on days 1, 3, and 5 of life. In adulthood (day 90), the animals were given prolonged E exposure with normal levels of testosterone (T) via T + E implants or empty capsules for 16 weeks. Prostates were examined histologically at 7 months. Rats treated neonatally to high-dose E with or without adult T + E had a high PIN incidence and score. Although low-dose neonatal E exposure alone mildly increased the PIN incidence/score, neonatal BPA alone had no pathologic alteration in the aged prostate. However, rats exposed neonatally to BPA followed by T + E in adulthood showed a significantly higher PIN incidence and score compared with controls, rats exposed only to BPA neonatally, or those given only T + E in adulthood (1). The PIN incidence and lesions in rats given BPA with adult T + E appeared similar to rats treated neonatally with high-dose E. Thus, the present

findings suggest that an environmentally relevant dose of BPA may increase the susceptibility of the prostate gland to carcinogenesis following additional adult exposures.

To determine whether neonatal exposures to estradiol or BPA may be mediated through epigenetic mechanisms, we screened these prostate tissues for global DNA methylation changes. Over 30 gene candidates were cloned that showed consistent methylation changes as a result of neonatal E or BPA exposures. Phosphodiesterase type 4, variant 4 (PDE4D4), the enzyme involved in degrading cAMP and regulating the cellular levels of this key cell-signaling molecule, was identified as a novel imprinted gene (1). In normal prostates, the 5' CpG island of PDE4D4 is gradually hypermethylated, and the gene is silenced with aging. Following neonatal BPA or estradiol exposure, PDE4D4 showed early and persistent hypomethylation of its 5' CpG island resulting in elevated PDE4D4 gene expression in the adult prostates. HPCAL, a gene that drives cAMP production, exhibited a specific methylation and expression alteration in neonatal BPA animals with aging. Together, these findings indicate that the prostate epigenome is permanently altered by early exposures to BPA, resulting in changes in gene expression. We hypothesize that this epigenetic alteration may be a molecular underpinning that leads to heightened predisposition to prostate carcinogenesis with aging.

## REFERENCE

1. Ho S-M, Tang W-Y, Belmonte J, Prins GS. Developmental exposure to estradiol or bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase 4. *Cancer Res* 2006;66: 5624–32.

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