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JOURNAL ARTICLE

Suppression of androgen action and the induction of gross abnormalities of the reproductive tract in male rats treated neonatally with diethylstilbestrol

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This study evaluated whether androgen action is altered in rats treated neonatally with diethylstilbestrol (DES) at a dose that induced reproductive tract abnormalities. Rats were treated on alternate days 2-12 with 10 microg DES and studied on Day 18. DES-induced abnormalities included a 70% reduction in testis weight, distension and overgrowth of the rete, distension and reduction in epithelial height of the efferent ducts, underdevelopment of the epididymal duct epithelium, reduction in epithelial height in the vas deferens, and convolution of the extra-epididymal vas. In DES-treated rats, androgen receptor (AR) immunoexpression was virtually absent from all affected tissues and the testis, whereas AR expression in controls was intense in epithelial and stromal cells. The DES-induced change in AR immunoexpression was confirmed by Western analysis for the testis. In rats treated neonatally with 1 microg DES, reproductive abnormalities were absent or minor, except for a 38% reduction in testis weight; loss of AR immunoexpression also did not occur in these rats. Treatment-induced changes in AR expression were paralleled by changes in Leydig cell volume per testis (91% reduction in the 10-microg DES group; no change in the 1-microg DES group). To test whether suppression of androgen production or action alone could induce comparable reproductive abnormalities to 10 microg DES, rats were treated neonatally with either a potent gonadotropin-releasing hormone antagonist (GnRHa) or with flutamide (50 mg/kg/day). These treatments reduced testis weight (68% for GnRHa, 40% for flutamide), and generally retarded development of the reproductive tract but failed to induce the abnormalities induced by 10 microg DES. GnRHa and flutamide caused no detectable change in AR immunoexpression in target tissues, with the exception of minor changes in the testes of flutamide-treated males. GnRHa treatment caused a reduction (83%) in Leydig cell volume comparable to that caused by 10 microg DES. Immunoexpression of estrogen receptor alpha (ER alpha) in the efferent ducts and of ER beta in all tissues studied were unaffected by any of the above treatments. Neonatal coadministration of testosterone esters (TE; 200 microg) with 10 microg DES prevented most of the morphological abnormalities induced by 10 microg DES treatment alone, though testis weight was still subnormal (46% reduction in DES + TE vs 72% in DES alone and 49% with TE alone) and some lumenal distension was still evident in the efferent ducts. Coadministration of TE with DES prevented DES-induced loss of AR immunoexpression

(confirmed for testis by Western blot analysis). It is concluded that 1) reproductive tract abnormalities induced in the neonatal male rat by a high (10 microg) dose of DES are associated with reduced AR expression and Leydig cell volume; 2) these changes are largely absent with a lower dose of DES (1 microg); 3) treatments that interfere with androgen production (GnRHa) or action (flutamide) alone failed to induce reproductive tract abnormalities or alter AR expression as did 10 microg DES; 4) a grossly altered androgen:estrogen balance (low androgen + high estrogen) may underlie the reproductive tract abnormalities, other than reduced testis weight, induced by high doses of DES.

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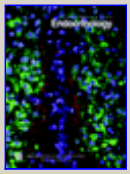

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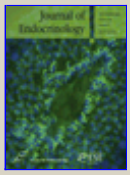

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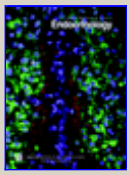

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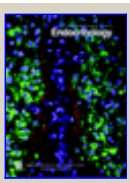

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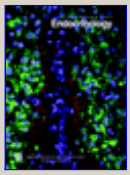

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