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Low androgen action at a critical time-point in the neonatal period down-regulates biomarkers for smooth muscle cell differentiation leading to permanent infertility

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Previously we showed that exposure of neonatal rats to estrogens and anti-androgens at a critical time period induced penile mal-development, characterized by accumulation of fat cells and loss of smooth muscle cells in the corpus cavernosum. This study aimed to determine the cellular and molecular changes characterizing the above effects. Pups were treated daily with GnRH antagonist antide or diethylstilbestrol (DES), with or without androgen receptor (AR) agonist dihydrotestosterone (DHT) or estrogen receptor (ESR) antagonist ICI 182,780, for postnatal days 1-6. Tissues were collected at days 7, 10, 21 or adulthood. Testicular testosterone (T) was assayed and microarray performed on the 7-day old penile and testicular samples. Real-time-PCR was used to quantify expression of *Ar*, *Esr1*, *Esr2*, *Pparg*, *Pde5a*, *Myh11* and *Acta2*. PDE5A, MYH11 and ACTA2 protein levels were determined by western blot and/or immunohistochemistry (IHC). Both estrogens and anti-androgens induced similar effects. Intratesticular T surge was decreased by 80-90%. The reduction was mitigated by ICI but not DHT co-administration. Microarray showed significant down-regulation of smooth muscle cell markers (*Myh11*, *Myh7*, *Mylk*, and *Actg2*) in the penis and steroidogenic enzymes (*Hsd3β1*, *Cyp11α1*, *Cyp17α1* and *Cyp2c22*) and Star protein in the testis. Real-time PCR showed 50-70% reduction in *Myh11* and *Pde5a*, which was confirmed by Western blots. ACTA2 IHC showed reduction in the number and size of corpus cavernosum's sinusoids. Contrastingly, *Pparg* and *Esr1* expression was up-regulated, while that for *Esr2* and *Ar* was unaltered. These results provide evidence that estrogen-induced penile mal-development is mediated via *ESR1* and AR pathways.

Biography

Lilian Okumu completed her PhD from University College Dublin, Ireland, and postdoctoral fellowship from Tuskegee University's Center for Veterinary Medicine, Nursing and Allied Health in 2013. Currently, she is an assistant professor of Biology at Tuskegee University.

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