Impact of testosterone therapy on urethral contractility and serotonin signaling in neuroendocrine cells through a cross-sex, transgender, and intersex lens

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INTRODUCTION AND OBJECTIVE: The full impacts of intersex conditions and gender affirming hormones for transgender people are unknown. We recently discovered that bacteria trigger a rare population of urethral cells to secrete serotonin and drive urethral contractions, expelling bacteria from the urinary tract. Estrus increases the strength of serotonin signaling, suggesting estrogenic control. The purpose of this study is to test the hypothesis that testosterone reduces urethral serotonin signaling and contractility, potentially sensitizing to urinary tract infection and increasing frequency of small volume spontaneous voiding (incontinence).

METHODS: Five- to eight-week-old adult female C57BL/6J mice were sham operated (control) or treated with a subcutaneous slow-release testosterone implant (25 mg). Six days after implant surgery, voiding behavior was quantified using the void spot assay. Seven days after implant surgery, urethras were collected from twelve mice per experimental group to compare contractile response to serotonin by wire myography (7) or real-time RT-PCR (5). Real-time RT-PCR will be used to compare urethra RNA abundance of key genes involved in serotonin biosynthesis (*Tph1*), serotonin reuptake from extracellular space (*Slc6a4*), and serotonin receptors (*Htr2b*, *Htr3a*, *Htr3b*, and *Htr4*). Cardiac blood was collected to quantify circulating concentrations of serotonin and testosterone.

ANTICIPATED RESULTS: Testosterone implants did not significantly change the frequency of small volume urinary voids. We expect testosterone will reduce the force of serotonin-mediated urethral contractions and the abundance of *Tph1*, or *Htr2b*, *Htr3a*, *Htr3b*, and *Htr4* and may increase the abundance of *Slc6a4*. We also expect that testosterone implants will increase circulating testosterone concentration and decrease circulating estradiol concentration; estradiol concentration likely has a play in results as well.

CONCLUSIONS: Testosterone may reduce urethral neuroendocrine cell signaling, which could trigger adverse outcomes of incontinence and increased susceptibility to UTI among people who assigned female at birth and under androgen therapy or have hormone-affected intersex conditions.

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