A neuroanatomical mechanism linking perinatal chemical exposure to prostate smooth muscle hyperactivity and altered voiding function

**Background:** The historical focus of male lower urinary tract dysfunction (LUTD) has been benign prostatic enlargement and other aging-related processes. Little attention has been directed towards the influence of early life events on urinary physiology in advanced age. Here, we identify the intrauterine environment as a modifier of adult voiding function and risk factor for male LUTD.

**Methods:** To model environmental chemical exposures, we exposed pregnant mice to the environmental contaminant 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD, 1 µg/kg), coinciding with initiation of lower urinary tract development in male fetuses. We aged male pups to embryonic day (E) 17.5, postnatal (P) day 9, and 14 weeks of age and collected prostate tissue to stain for noradrenergic axons via immunohistochemistry. RNAseq was performed on E16.75 fetal prostates to identify dysregulated neurotrophic factors. Prostate muscle sensitivity was measured using genetically encoded calcium receptors and tissue bath. Urinary frequency was measured using cystometry.

**Results:** Fetal TCDD exposure incites abnormal urodynamics in adult male mice, including increased urinary voiding frequency. TCDD also enhances adult prostate sensitivity to electrically evoked muscle contraction, suggesting increased autonomic tone. IUL TCDD exposure stably increases noradrenergic axon density beginning in the fetal period and persisting into adulthood. These changes are accompanied an increase in the abundance of a neurotrophin, Artemin (*Artn*), in the fetal prostate.

**Conclusions:** This is the first evidence that intrauterine chemical exposures can reprogram prostate neuroanatomical development and drive prostatic smooth muscle hyperactivity in adulthood, which may create a susceptible phenotype for aging-related male lower urinary tract dysfunction.