The role of Urethral Neuroendocrine cells in Urinary Tract Infection
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Urinary tract infections (UTIs) occur in 50–60% of adult women in the United States

What is the role of the urethra?

Ascending Urinary tract infection

E.Coli (LPS)

Urethra

E. coli

The objectives of this study are to test the hypothesis that lipopolysaccharide (LPS), a component of the bacterial cell wall, drives urethral smooth muscle contraction in a serotonin receptor HTR2B-dependent fashion. We will also test the hypothesis that the presence of neuroendocrine cells in mice affords protection against infection by ascending E. coli UTI89.

Methods and Results:
A) Contractility of isolated adult female mouse urethras will be evaluated in response to graded concentrations of LPS, serotonin, and BW 723C86 (an agonist of the serotonin receptor HTR2B). Contractility assays will be conducted in the presence of guanethidine, a drug that inhibits neurotransmitter release from axons, to test the hypothesis that LPS and serotonin mediate their actions in an axon-independent fashion.
We expected that LPS, serotonin and BW 723C86 will drive urethral smooth muscle contraction.

A)

LPS
Serotonin
BW 723C86

Evaluation of Contractility

Urethral smooth muscle contraction

B) We will create mice that are deficient in urethral neuroendocrine cells by breeding Shh-cre with a conditional null allele of achaete-scute homolog 1 (Ascl1), a gene required for neuroendocrine cell differentiation. We will instill E. coli UTI89 into the caudal urethra of Ascl1 conditional null and wild type control mice via a catheter to initiate an ascending infection. We will test whether mutant mice have more E. coli (CFUs) and more inflammation (CD45+ cells) in urethra and bladder than infected wild type control mice. We expect Ascl1 conditional null mice will experience more severe E. coli infection than control mice.

B) Female Wild Type (control)

Female Shh-cre Ascl1

Severe inflammation?

Positive

Increase E.coli?

Positive

C) SSRI - FLUOXETIN

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TREATMENT

Reduce infection/inflammation

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C) We will test whether treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine, which prevents reuptake of secreted serotonin in the lower urinary tract and elsewhere, increases sensitivity to LPS-mediated contraction in vitro and reduces severity of infection from instilled E. coli in vivo.
We predict fluoxetine treatment will increase serotonin-driven muscle contraction in vitro and reduce severity of LUT infection and inflammation in vivo.

Conclusions:
We expect to establish a key role for urethral neuroendocrine cells in protecting against ascending E. coli infection.
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Figure 1 Urethral epithelial cells positive for serotonin. Wild type female was euthanized via CO2 asphyxiation. Bladder and urethra were dissected fixed in formalin and then placed in arrays before embedding in paraffin. Immunohistochemical staining for E-cadherin (green) and Serotonin (white) was performed. Slide was also stained with DAPI (blue) so that nuclei of individual cells could be identified. The slide was imaged at 20X.