

SILDENAFIL REDUCES DETRUSOR HYPERTROPHY AND FIBROSIS IN A MOUSE MODEL OF BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Bladder fibrosis ensuing from chronic obstructive injury is a maladaptive process involving activation of fibroblasts, influx of inflammatory cells, cellular regeneration, deformations of extracellular matrix, and alterations in collagen deposition. Resultant anatomic remodeling culminates in a loss of bladder distensibility and diminished compliance. Recent clinical evidence suggests that sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor employed to reverse dysfunction associated with obstructed cardiomyopathy and lung fibrosis, can ameliorate bladder obstructive symptoms. Herein we sought to investigate tissue specific expression of PDE-5 and the effect of sildenafil on bladder hypertrophy and fibrosis in an experimental model of bladder outlet obstruction (BOO).

Study design, materials and methods

Partial BOO was performed in oophorectomized female mice by periurethral injection of rat tail collagen. Tissues were harvested at 1 week for relative mRNA expression analysis. Unobstructed animals were utilized for determination of PDE-5 activity by ion-exchange chromatography. At 8 weeks, sildenafil citrate (4 mg/kg) was administered by intraperitoneal injection 3 times per week. Urodynamics were performed at 16 weeks prior to genitourinary organ harvest for histology and molecular analysis.

Results

Isoforms of PDE 1, 4 and 5 were expressed in the genitourinary tract of both male and female mice and mRNA levels were independent of short-term outlet obstruction. PDE-5 enzyme isolated from bladder lysates specifically bound cyclic GMP and was selectively inhibited by sildenafil. Periurethral obstruction resulted in smooth muscle hypertrophy, lamina propria thickening, increased collagen deposition and inflammatory cell influx. Following sildenafil treatment, histology revealed diminished hypertrophy and inflammation, confirmed with a decline of IL-6 levels. Mean bladder capacity of unobstructed mice was 206 cc which decreased to 96 cc following obstruction. Sildenafil treatment rescued capacity to 147cc.

Interpretation of results

These preliminary data revealing substantial expression of PDE-5 and additional PDE isoforms within the mouse genitourinary system suggest sildenafil specifically interacts with bladder PDE-5 and contributes to reversal of detrusor hypertrophy and fibrosis.

Concluding message

These results provide a critical foundation for exploration of the role of PDE-5 inhibitors in bladder inflammation and fibrosis in an experimental model of BOO. Significant expression of isoforms of PDE in addition to PDE-5 opens possibilities for therapeutic use of alternate inhibitors to prevent or reverse bladder fibrosis. Future studies aimed at exploring the fundamental signalling pathways influenced by PDE-5 inhibition in regards to the inflammatory and hypertrophic changes promise substantial potential for evolution of our mechanistic understanding of BOO and BPH as well as novel urologic therapeutics.

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<i>What were the subjects in the study?</i>	ANIMAL
<i>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</i>	Yes
<i>Name of ethics committee</i>	IACUC and IRB