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SOLIFENACIN SUCCINATE REVERSES URODYNAMIC AND DETRUSOR CHANGES ASSOCIATED WITH BLADDER OUTLET OBSTRUCTION – A MOUSE MODEL

Hypothesis / aims of study

Bladder outlet obstruction (BOO) can result in bothersome storage and voiding symptoms and may be associated with urodynamic and histological changes. Treatment of benign prostatic hyperplasia (BPH) typically focuses on reducing outlet resistance, aiming to reverse the compensatory bladder changes. Recently, the use of detrusor-directed pharmacotherapy with antimuscarinics in men with BPH has gained popularity, based on short-term safety and efficacy. In addition, it has been demonstrated that detrusor-directed treatment with a phosphodiesterase type 5 inhibitor can *prevent* the structural and functional detrusor changes that occur in a mouse model of bladder outlet obstruction [1], and that solifenacin succinate can similarly *prevent* those detrusor changes [2]. We aim now to determine if treatment with solifenacin can *reverse* the structural and functional changes that occur with BOO in a mouse model.

Study design, materials and methods

We partially obstructed the urethra in 24 Balb/CAN mice. A 4-0 nylon suture was tied loosely around the urethra, using a PE-50 tubing as a guide to prevent over-obstruction. Mice were survived for 12 weeks. Half of the mice were given 6 wks of oral solifenacin succinate (1 mg/kg/d) starting 6 weeks post-obstruction, and half were not. 12 mice served as untreated controls. Urodynamics were performed at baseline and after 12 weeks, with measurement of detrusor pressure (P_{det}) at capacity, and volume at first uninhibited bladder contraction as a percent of capacity (V_{DO1}). Bladders were harvested, weighed, fixed, and stained with trichrome and hematoxylin and eosin (H&E). Histologic scoring was performed in blinded fashion by 2 pathologists and 2 urologists. H&E scoring was used to evaluate detrusor muscle thickness, with a score of 1 for atrophy (< 100 µm thick at the mid-body of the bladder), 2 for normal appearing bladder (100–200 µm thick at the mid bladder body), and 3 for hypertrophy (> 200 µm thick at the mid bladder body). The bladders were compared with slides of a normal bladder from six untreated, unobstructed male Balb/CAN control mice (typical thickness 100–200 µm). Trichrome staining was scored in a similar manner, with a score of 1 for decreased collagen, 2 for normal collagen, and 3 for increased collagen deposition in the lamina propria and detrusor muscle compared with the normal bladder slides from the six control mice. A consensus score was reached among the three examiners for each specimen.

Results

Compared to controls, BOO mediated a decrease in VDO1 (median=34.6% vs 53.5%. p=0.03), and an increase in bladder mass (85.6 ± 9.2 vs 30.8 ± 3.5 mg, p=0.02), detrusor hypertrophy (median=3.0 vs 2.0, p=0.02), and fibrosis (median=3.0 vs 2.0, p=0.02). Compared to untreated BOO mice, delayed treatment with solifenacin mediated an increase in VDO1 (68.0% vs 34.6%, p<0.01), a reduction in bladder mass (56.5 ± 3.8 vs 85.6 ± 9.2 mg, p=0.03), reduced detrusor hypertrophy (median=2.0 vs 3.0, p=0.01), but did not reduce fibrosis (median=3.0 vs 3.0, p=0.6).

Urodynamic and Histological Comparisons Among Groups

Group	Mean Weight (gm)	Mean P_{det} (mm Hg)	Median V_{DO1}	H&E score	Trichrome score
CTRL	30.8 ± 3.5	12 ± 2	53.5%	2	2
BOO	85.6 ± 9.2	29 ± 2	34.6%	3	3
BOO + solifenacin	56.5 ± 3.8	24 ± 3	68.0%	2	3

CTRL = control
BOO = bladder outlet obstruction, no solifenacin
BOO+ solifenacin = Bladder outlet obstruction plus solifenacin at 6 weeks x 6 weeks
P_{det} = detrusor pressure during voiding
V_{DO1} = volume at first uninhibited contraction

Interpretation of results

Obstruction of the bladder outflow typically induces remodeling of urinary bladder smooth muscle, and smooth muscle hypertrophy. These structural changes and associated alterations in bladder function are an important mediator of the bothersome LUTS associated with BPH. Detrusor hypertrophy and increased detrusor contractility can result from increased voiding pressure, as well as from increased detrusor overactivity. BOO can lead to detrusor ischemia, affecting the function and structure of the obstructed bladder [3]. We hypothesize that solifenacin improves detrusor storage function and partially reverses detrusor hypertrophy in a rodent model of BOO by reducing the detrusor overactivity that results from urethral obstruction. Addition of solifenacin did not affect detrusor contractility during voiding, and BOO remained constant with the nylon tie around the urethra. The collagen deposition was not improved in this study, perhaps because of too short a time frame, or more likely due to the relative irreversibility of the detrusor fibrosis.

Concluding message

In a mouse model of established BOO, treatment with six weeks of oral solifenacin appeared to *reverse* some of the urodynamic and histologic changes that occur with untreated BOO. BOO was associated with increased detrusor overactivity, bladder mass, detrusor hypertrophy, and collagen deposition. Treatment with solifenacin succinate resulted in an improvement in detrusor overactivity, and partially reversed the detrusor hypertrophy, but did not appear to reverse fibrosis. With the prevalent use of antimuscarinics in men with BPH and bothersome storage symptoms, a human trial with evaluation of changes in urodynamic parameters and bladder wall thickness may help to further establish the role of detrusor-directed treatment in men with BOO.

References

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