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SACRAL NERVE STIMULATION PREVENTS THE FUNCTIONAL AND STRUCTURAL CHANGES ASSOCIATED WITH BLADDER OUTLET OBSTRUCTION: A RAT MODEL

Hypothesis / aims of study

Lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE) are prevalent in the aging male population. It is well established that BPE can lead to bladder outlet obstruction (BOO), resulting in both structural and functional changes to the detrusor. Gross structural changes in the bladder, such as smooth muscle hypertrophy and fibrosis have been shown to accompany bladder outlet obstruction, as have functional (urodynamic) changes – such as increased detrusor overacitivty. Medical therapy with alpha-adrenergic receptor blockers and/or 5-alpha reductase inhibitors are currently the standard treatments for symptomatic BPE, with de-obstructive surgery for patients who fail pharmacotherapy. Because bothersome storage symptoms often co-exist with BPE, there has been increasing interest in detrusor-directed therapy, in particular with antimuscarinic medications. Recent investigations have established the short-term efficacy of treating bothersome storage symptoms in men with BOO with such detrusor directed therapy. Sacral nerve stimulation (SNS) is a well-established technique, with proven efficacy for treating patients with refractory urinary frequency, urgency or urge incontinence. Since SNS is thought to act primarily via afferent neuromodulation, and does not interfere with normal micturition, we hypothesize that SNS may be efficacious in ameliorating the bothersome storage symptoms in men with BOO, without interfering with bladder emptying. We investigate the effect of sacral neuromodulation in preventing the structural and functional changes that occur in a bladder in a rat model of BOO.

Study design, materials and methods

24 female Sprague-Dawley rats (250 gm) were divided into 4 groups: control (CTRL), BOO, SNS, and both (BOO/SNS). BOO was achieved by partially occluding the proximal urethra. SNS was accomplished by stimulating the S1-S4 dorsal roots with a unipolar S1 lead, 8 hours daily. Urodynamics were performed at baseline and after 6 weeks, with measurement of bladder capacity, voiding pressure, volume at first uninhibited bladder contraction. Bladders were harvested, weighed, stained, and scored for detrusor hypertrophy and fibrosis. Histological scoring was performed in blinded fashion by 2 pathologists and 1 urologist. H & E scoring was used to evaluate detrusor muscle thickness, with a score of 1 and 2 for atrophy (1= < 50μm, 2= 50-100 μm thick at the mid-body of the bladder), 3 for normal appearing bladder (100-150 μm thick at the mid bladder body), and 4 and 5 for hypertrophy (4=150-250 μm, 5=>250 μm thick at the mid bladder body). The bladders were compared to slides of a normal bladder from 6 untreated control rats (typical thickness 100-150 μm at mid bladder body). Trichrome scoring was performed in a similar manner, with a score of 1-2 for decreased collagen, 3 for normal collagen, and 4-5 for increased collagen deposition in the lamina propria and detrusor muscle when compared to the normal bladder slides from the 6 control rats. A consensus score was reached among the three examiners for each specimen.

Results

BOO mediated an increase in bladder weight (377 ± 5 mg vs 88 ± 5 mg, p = 0.01), an increase in mean voiding pressure (P_{det}=35 ± 2 mm Hg vs. 23 ± 2 mm Hg, p=0.02), an increase in mean bladder capacity (C=1230 ± 250 μl vs. 484 ± 60 μl, p=0.08), and a decrease in mean volume at first unstable bladder contraction (V_{DO1} = 67 ± 16 μl vs. 110 ± 247 μl, p=0.02) compared to CTRL. Addition of SNS did not significantly affect P_{det} (30 ± 3 mm Hg vs. 35 ± 2 mmHg, p=0.2), but decreased C (630 ± 90 μl vs. 1230 ± 250 μl, p=0.05), increased V_{DO1} (628 ± 91 μl vs. 67 ±16 μl, p=0.002), and trended toward a decreas in bladder weight 268 ± 10 mg vs 377 ± 5 mg, p=0.08) compared to BOO. Detrusor hypertrophy and fibrosis were both significantly greater in BOO vs. CTRL and BOO vs. BOO/SNS.

Urodynamic and Histological Comparisons Among Groups

Group	Mean Weight (mg)	Mean Capacity (μl)	Mean P_{det} (mm Hg)	Median V_{DO1}	H&E score	Trichrome score
CTRL	88 ± 5	484 ± 60	23 ± 2	110 ± 24	3	3
BOO	377 ± 5	1230 ± 250	35 ± 2	67 ± 16	5	5
BOO+SNS	268 ± 10	630. ± 90	30 ± 3	628 ± 91	4	3

SNS = sacral nerve stimulation
CTRL = sham-operated only
BOO = bladder outlet obstruction, no SNS
BOO+ SNS = bladder outlet obstruction plus SNS
P_{det} = detrusor pressure during voiding
V_{DO1} = volume at first uninhibited contraction

Interpretation of results

Obstruction of the bladder outflow typically induces remodelling 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 BPE. Increased detrusor contractility can result from increased voiding pressure, as well as from increased detrusor overactivity. Uninhibited non-voiding contractions (resulting in isovolumetric bladder contractions during the storage phase) lead to increased detrusor contractility and detrusor muscle hypertrophy [1]. BOO can lead to detrusor ischemia, affecting

the function and structure of the obstructed bladder [2]. In addition, the diminished blood flow and oxygen tension in the detrusor secondary to BOO may be worsened by increases in detrusor pressure during uninhibited bladder contractions during the filling phase [3]. We hypothesize that SNS improves detrusor storage function and prevent detrusor hypertrophy and collagen deposition in a rodent model of BOO, by preventing the uninhibited bladder contractions the result from obstruction. Our animal model demonstrated that treatment of BOO mice with SNS mediated a decrease in detrusor overactivity (measured by V_{DO1}). However, there was no significant change in voiding pressure, as the increased urethral resistance remained unaltered, and the fact that afferent neuromodulation does not typically affect detrusor contractility.

Concluding message

Partial BOO caused functional and structural changes in the detrusor. BOO mediated increases in bladder capacity and in detrusor overactivity, which were prevented by SNS. However, SNS in obstructed rats did not adversely affect detrusor contractility. In addition to these functional changes, SNS decreased the detrusor muscle hypertrophy and fibrosis caused by partial BOO. SNS appears to prevent the functional and structural changes that result from partial BOO in a rat model. Human studies may be indicated to investigate the role of SNS in men with prostatic obstruction.

References

1. Sullivan MP, DuBeau CE, Resnick NM, Cravalho EG, Yalla SV: Continuous occlusion test to determine detrusor contractile performance. J Urol 1995; 154: 1834-40
2. Azodzoi KM, Keim VK, Tarcan T, Siroky MB. Alteration of urothelial-mediated tone in the ischemic bladder: role of eicosanoids. Neurourol Urodyn 2004; 23: 258–64
3. Greenland JE, Hvistendahl JJ, Andersen H et al. The effect of bladder outlet obstruction on tissue oxygen tension and blood flow in the pig bladder. BJU Int 2000; 85: 1109–14

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