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URETHRAL UROTHELIAL DYSFUNCTION AND ALTERED EPITHELIAL FUNCTIONAL PROTEINS AND ALPHA-ADRENOCEPTOR IN MALE PATIENTS WITH BLADDER NECK DYSFUNCTION AND BPH

Hypothesis / aims of study
Urethral function plays an increasing role in many lower urinary tract diseases, which was overlooked before. The cause of bladder neck dysfunction (BND) has not been clarified clearly, and functional bladder outlet obstruction (BOO) or neurologic theories have been suggested. In both urethra and bladder, urothelium serves not only a physical barrier but also a sensor and transducor of signaling. We speculated that urothelial dysfunctions and altered expressions of epithelial functional proteins might play important roles in the pathogenesis of BND and BPH.

Study design, materials and methods
Male patients with BOO necessary for the surgical treatment, including 10 BND and 12 BPH patients were collected as well as 3 controls (bladder tumor). Strips of urethra tissue from bladder neck to verumontanum were resected between 5 to 7 o'clock of urethra during the operations of transurethral resection of bladder neck, prostate, or bladder tumor. Resected urethral tissue was divided into Zone 1 (intravesical part of bladder neck), Zone 2 (urethral part of bladder neck), and Zone 3 (prostatic urethra) for analysis. Immunofluorescence staining of E-cadherin and zona occuldens-1 (ZO-1) and Western blotting analysis of α1 adrenoreceptor and β3 adrenoreceptor of the urethra specimen were performed.

Results
BND patients had a significant smaller size of prostate than BPH patients (Table 1). In immunofluorescence staining of either E-cadherin or ZO-1, there was no significant difference among these groups of patients. In BND patients, Zone 1 had a significant lower expression of E-cadherin than Zone 3 (p=0.050), and similar condition was also found in BPH patients (p=0.034). In Western blotting analysis, BND patients had non-significantly increased expressions of α1 adrenoreceptor in each part of urethra versus BPH patients or controls. In both BND and BPH patients, their Zone 1 and Zone 2 had significantly lower expressions of β3 adrenoreceptor than the respective parts in controls. There was no significant difference of either α1 adrenoreceptor or β3 adrenoreceptor among different parts of urethra within each subgroup patients.

Interpretation of results
BND patients had a non-significantly increased (probably due to small case number) expression of α1 adrenoreceptor in urethra versus BPH patients or controls, which indicated the functional obstruction theory by the contraction role of α1 adrenoreceptor other than the anatomic obstruction theory by prostate compression in some BPH patients. The role of β3 adrenoreceptor in urinary bladder involves in decreased bladder afferent firing and relaxation, but that in urethra is not clear. In the present study, both BND and BPH patients had significantly lower expressions of β3 adrenoreceptor in bladder neck than controls. It suggested the role of β3 adrenoreceptor in urethral relaxation and its dysfunction might contribute to voiding dysfunction and/ or BOO, in which high intravesical/ voiding pressure resulted in the bladder/ urethra urethelial dysfunction (lower expression of E-cadherin in the intravesical part of BN in comparison with prostatic urethra). In summary, the bladder neck of BOO men had a distinct pattern of lower expression of β3 adrenoreceptor and E-cadherin than controls, suggesting its importance.

Concluding message
Altered expressions of adrenoreceptors with urethral dysfunction may have an important role in the pathophysiology of male BOO, especially in patients with BND/ small prostate size. The bladder neck of BOO men had a distinct pattern of urothelial dysfunction (lower E-cadherin) and altered adrenoreceptor expressions (lower β3 adrenoreceptor) than controls, suggesting its importance different from the other parts of urethra.

Table 1. Demographics and the expressions of epithelial functional proteins and alpha-adrenoceptor in BND, BPH patients and control

	BND	BPH	Control	P value[#]
Number	10	12	3	
Age	69.0 ± 10.0	71.6 ± 11.0	72.7 ± 10.8	0.575
TPV (mL)	22.88 ± 4.10	67.15 ± 35.3		0.003
TZI	0.31 ± 0.08	0.45 0.14		0.067
Immunofluorescence straining				
E-cadherin				
Zone 1	4.603 ± 8.252	3.837 ± 5.164	4.135 ± 0.437	0.793
Zone 2	3.208 ± 5.665	7.770 ± 9.433	0.000 ± 0.000	0.196
Zone 3	7.608 ± 11.390	5.684 ± 4.696*	0.000 ± 0.000	0.598
ZO-1				
Zone 1	12.261 ± 6.107	15.115 ± 5.123	11.472 ± 1.422	0.247
Zone 2	11.057 ± 9.646	14.437 ± 6.113	16.957 ± 7.954	0.330
Zone 3	12.092 ± 5.648*	14.817 ± 7.694	20.723 ± 7.257	0.364
Western blotting analysis				
Number	4	9	3	
α1 adrenoreceptor				
Zone 1	1.768 ± 0.974	1.117 ± 0.447	1.290 ± 0.437	0.116
Zone 2	1.628 ± 0.272	1.139 ± 0.497	1.470 ± 0.295	0.096
Zone 3	2.750 ± 2.366	1.407 ± 0.648	1.453 ± 0.633	0.127
β3 adrenoreceptor				
Zone 1	0.448 ± 0.235*	0.677 ± 0.391*	1.103 ± 0.483	0.331
Zone 2	0.528 ± 0.206*	0.678 ± 0.338*	1.130 ± 0.410	0.651
Zone 3	0.465 ± 0.240	0.569 ± 0.306	0.477 ± 0.439	0.313

TPV: total prostatic volume; TZI: transitional zone index
Zone 1: Intra-vesical (trigone) part of bladder neck
Zone 2: Urethra part of bladder neck
Zone 3: Prostatic urethra
[#]: P value between BND and BPH
*: P value < 0.05 versus control.

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