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UROTHELIAL DYSFUNCTION AND ALTERATIONS OF SENSORY PROTEIN EXPRESSIONS IN BLADDER MUCOSA IN PATIENTS WITH IDIOPATHIC DETRUSOR UNDERACTIVITY

Hypothesis / aims of study
Detrusor underactivity (DU) can be observed in many neurogenic condition and myogenic failure. The pathomechanism of DU is indefinite , but impaired bladder sensory pathway affecting the activation of detrusor contraction is considered a possible cause. In addition, urothelial dysfunction and dysregulated protein expression in bladder mucosa are proved in many lower urinary tract diseases (LUTDs). This study investigated the potential urothelial dysfunction and proteins expressed in bladder mucosa in DU patients

Study design, materials and methods
Bladder wall biopsies were performed in 35 idiopathic DU patients, and 10 controls. Immunofluorescence (IF) staining of zona occuldens-1 (ZO-1) and E-cadherin in urothelium, and tryptase and TUNEL (indicating mast cells and apoptotic cells respectively) in suburothelium were performed. Western blotting analysis of proteins in bladder mucosa including P2X3, M2 and M3 muscarinic receptors, β-3 adrenoreceptor, and endothelial nitric oxide synthase (eNOS) were done. DU patients were compared with controls in the apsects of protein expressions.

Results
DU patients included 23 women and 12 men with a mean age of 55.8 ±19.6 years. In IF staining, DU patients had a signficant lower expression of E-cadherin but not ZO-1 in urothelium, and higher mast cell and apoptotic cell numbers in suburothelium than controls (Fig. 1, Table 1). In Western bloting analysis of bladder mucosa, DU patients had signficant lower expression of M2 receptor, P2X3 receptor, and eNOS in bladder mucosa than controls but not M3 receptor or β-3 adrenoreceptor (Table 2). Reversed M2/M3 receptor ratio was also observed in DU patients.

Interpretation of results
In many LUTDs including detrusor overactivity (DO), defective E-cadherin with increased suburothelial inflammation and apoptosis are found and considered to be associated with bladder inflammation. DU patients has the similar inflammatory characteristics. DO patients presenting with involuntary detrusor contraction have increased P2X3 and eNOS expressions in bladder mucosa. M2 muscarinic receptor in bladder mucosa plays an important role of bladder afferent activation that enhancing DO. E-cadherin is not only an adhesive protein functioning as a barrier but also associated with bladder sensation through the connection of TRPV4. In DU patients, we found an indistinct pattern of decresed expression of sensory proteins including E-cadherin in urothelium, P2X3, eNOS, and M2 muscarinic receptors in bladder mucosa. It indicated that the impaired urothelial signaling and sensory pathway were associated with the inactivation of detrusor contraction, which might cause DU.

Concluding message
Urothelial dysfunction, increased suburothelial inflammation, and alternations of sensory proteins expression in bladder mucosa in DU patients were found. Impaired urothelial signaling and sensory tranduction pathway is a probable cause of DU.

Table 1. Immunoflurescent and Western blots analysis of proteins in bladder mucosa in DU patients and controls

	Control	DU	P value
Number	10	35	
Sex	10 Female	23 Female, 12 male	
Age	52.4 ± 10.5	55.8 ± 19.6	0.783
Immunoflurescent analysis			
E-cadherin	41.3 ± 8.4	21.1 ± 18.6	0.002
Tryptase	5.9 ± 4.9	10.6 ± 5.6	0.027
TUNEL	1.0 ± 1.4	6.2 ± 3.2	<0.001
ZO-1	6.4 ± 1.7	7.9 ± 3.4	0.212
Western blots analysis			
M2 receptor	1.22 ± 0.59	0.32 ± 0.23	0.014
M3 receptor	1.47 ± 1.07	1.2 ± 0.81	0.585
M2/M3 receptor ratio	2.99 ± 6.9	0.46 ± 0.39	0.076
β-3 adrenoreceptor	0.46 ± 0.56	0.71 ± 0.29	0.420
P2X3	1.66 ± 1.17	0.26 ± 0.28	0.010
eNOS	0.34 ± 0.17	0.08 ± 0.07	0.018

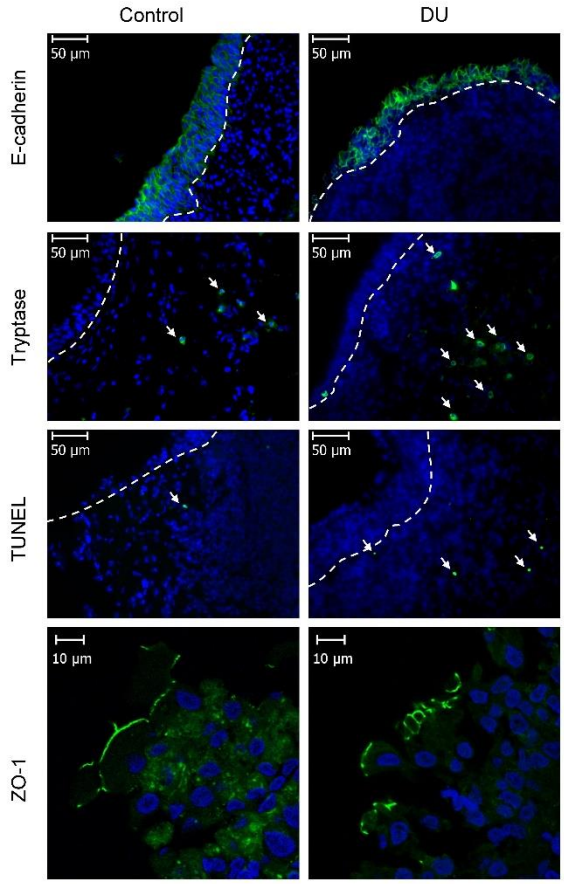

Fig. 1. Immunofluroescence staining of the bladder mucosa in DU patients and controls.

Disclosures
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