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THE ROLE OF STRESS ASSOCIATED RECEPTOR AND NEUROTROPHIN EXPRESSION IN UROTHELIUM OF INTERSTITIAL CYSTITIS

Hypothesis / aims of study
Previous studies showed the symptoms aggravation with stress in the patients with interstitial cystitis/bladder pain syndrome (IC/BPDS). Sensory hyperinnervation was also found in the IC/BPS bladder. However, the pathogenesis pathway was still unclear. The aim of current study is to investigate the stress associated receptors and neurotrophin expression in the urothelium of IC/BPS patients.

Study design, materials and methods
The patients with IC/BPS who were admitted to our hospital for cystoscopic hydrodistention were recruited into this study. These patients were classified into ulcer and non-ulcer IC/BPS according to the cystoscopic finding of Hunner's lesion. Random cold-cup biopsies of the posterior bladder wall in these patients were obtained after cystoscopic hydrodistention. Western blotting with quantification was used to investigate the expression of neurotrophin growth associated protein 43 (GAP-43), nerve growth factor (NGF) and its receptor tropomyosin receptor kinase A (TrkA) in these bladder specimens. The stress associated receptor, corticotropin releasing factor receptor (CRFR) 1 and 2, were also investigated with western blotting. Fluorescent immunochemical staining was also performed to verify the location of CRFR1 expression in the urothelium. Bladder specimens from female patients with stress urinary incontinence were also obtained for western blotting and were considered as normal control. Pearson's correlation coefficients were calculated to determine the correlations between the quantification results of western blotting and clinical symptoms scores, including Interstitial Cystitis Symptoms and Problem Index (ICSI and ICPI), Visual Analogue Scale for pain (VAS).

Results
A total of 62 IC/BPS patients (23 ulcer IC/BPS and 39 non-ulcer IC/BPS) and 24 normal controls were enrolled. The patients with non-ulcer IC/BPS were younger than ulcer IC/BPS and controls. Among 3 groups, the western blotting revealed the urothelium in the ulcer IC/BPS had significantly higher expression NGF, Trk-A and CRFR1 (Table 1, Fig. 1). The urothelium CRFR2 also significantly decreased in the ulcer IC/BPS. The GAP-43 expression was significantly lower in the non-ulcer IC/BPS. Among all IC/BPS patients, the CRFR2 expression was significantly negative correlated with ICSI, ICPI and VAS (r=-0.362.-0.439, -0.372; p-value= 0.017, 0.003, 0.014, respectively). The NGF expression in the urothelium was significantly correlated with the maximal bladder capacity, cystometric bladder capacity and CRFR1 (r=-0.272, -0.310 and 0.482; p=0.034, 0.028, 0.001, respectively). The immunochemical staining also revealed CRFR1 expression in the cell membrane of in the urothelium of IC/BPS patients (Fig. 2).

Table 1. Urothelium neurotrophin and stress associated receptors expressions in controls and IC/BPS patients

	(A) Control N=24	**(B) Non-ulcer IC/BPS N=39**	**(C) Ulcer IC/BPS N=23**	**p-value***
Age	57.00±12.78	48.10±12.28	59.91±10.04	<0.001 A vs B=0.019 B vs C=0.001 A vs C=0.703
NGF	0.83±0.61	0.50±0.34	1.32 ± 0.79*	<0.001 A vs B=0.090 B vs C<0.001 A vs C=0.016
TrkA	0.11±0.08	0.05±0.06	0.25± 0.30	<0.001 A vs B=0.438 B vs C<0.001 A vs C=0.014
GAP-43	0.65±0.32	0.48±0.37	0.93 ± 0.71	0.003 A vs B=0.395 B vs C=0.003 A vs C=0.145
CRFR1	1.14±0.52	1.42±1.97	2.90 ± 1.43	<0.001 A vs B=0.783 B vs C=0.002 A vs C=0.001
CRFR2	0.55±0.45	0.35±0.51	0.21 ± 0.32	0.041 A vs B=0.231 B vs C=0.533 A vs C=0.044

* p-value in one-way ANOVA and post hoc tests

Fig. 1. The Western blotting stress associated receptor and neurotrophin in IC/BPS and controls urothelium

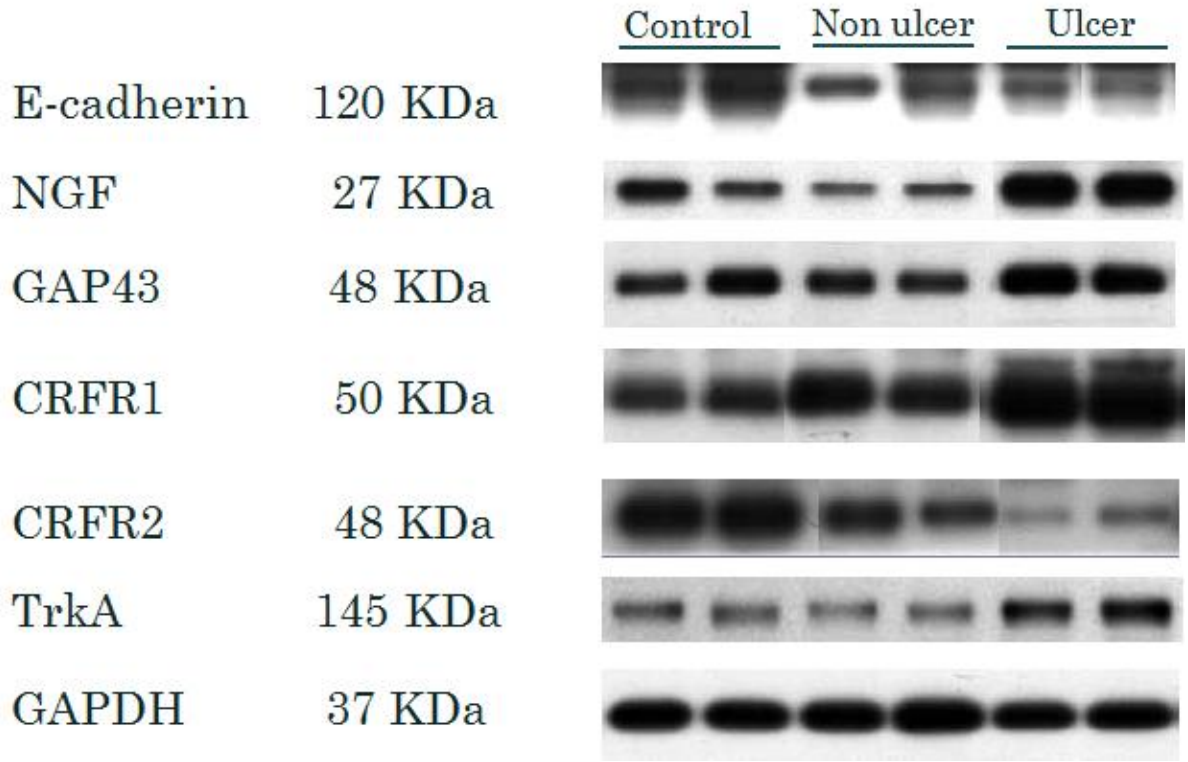
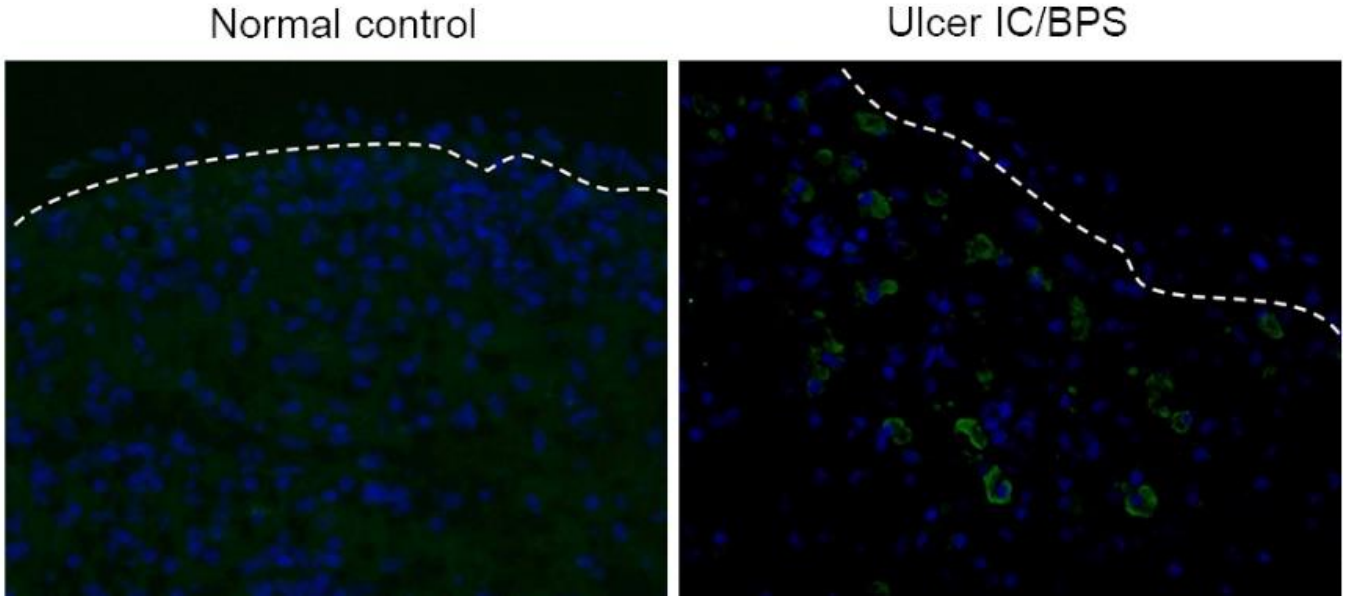


Fig. 2. The immunochemical staining for CRFR1 in IC/BPS ad controls urothelium



Interpretation of results

Current study revealed higher urothelium expression of NGF and Trk-A in the ulcer IC/BPS bladder than that in non-ulcer IC/BPS and controls. The NGF was also significantly correlated with small bladder capacity in the IC/BPS patients. It suggests neurotrophin and neuroplasty may involve the pathogenesis of IC/BPS. Previous studies showed opposite effects of CRFR1 and CRFR2 in central nerve system and gastrointestinal tract. Our study also revealed increased CRFR1 and decreased CRFR2 expression in the urothelium of ulcer IC/BPS bladder. CRFR2 expression was negative correlated severe symptoms score. Stress associated receptors may play an important role of in the pathogenesis of IC/BPS.

Concluding message

Neurotrophin and stress associated receptors expression levels were significantly increased in the ulcer IC/BPS patients, and were significantly correlated with clinical symptoms. Neurotrophin and stress associated receptors may play an important role of in the pathogenesis of IC/BPS.

Disclosures

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