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MOLECULAR BASIS OF URGENCY: VANILLOID RECEPTOR EXPRESSION IN THE HUMAN BLADDER

Hypothesis / aims of study

Urgency for fear of leakage is the cardinal symptom of the overactive bladder syndrome, and is commonly caused by urodynamically identifiable detrusor overactivity. Urgency is also experienced by other groups of patients such as those with painful bladder syndrome (PBS) where urgency is not associated with detrusor overactivity. Treatments targeting vanilloid receptors (TRPV1) are effective in the treatment of some bladder disorders. Since TRPV1 participate in the afferent arm of voiding reflex arcs [1], we hypothesised that TRPV1 might be involved in the sensation of urgency. The aim of the study was to determine the expression profiles of TRPV1 mRNA in defined bladder regions of patients with painful bladder syndrome (PBS) compared with overactive bladder (OAB) syndrome.

Study design, materials and methods

PBS patients met the following criteria: 1) a symptom complex of at least 6 months, which typically involved recurrent episodic urethral discomfort, and burning or stinging on or after voiding; 2) frequency and nocturia; 3) absence of urinary tract infection (UTI) or other obvious pathology; 4) no bladder pain; 5) pressure on the trigone on vaginal examination reproduced their discomfort; 6) inflammatory changes localized to the trigone and bladder neck were the only cystoscopic finding; and 7) normal filling cystometry with variable reduction of maximum cystometric capacity, and an early first sensation of bladder filling due to sensory discomfort, which could not be dispelled, were demonstrated urodynamically.

Women with OAB syndrome had symptoms of frequency, urgency and nocturia, associated with urge incontinence (OAB wet). These patients had urodynamically proven IDO (uninhibited phasic contractions) and were refractory to treatment with ≥2 anticholinergic drugs.

Control biopsies were obtained from body and trigone of age-matched women undergoing check cystoscopy for previous bladder cancer or asymptomatic microhematuria.

Cold-cup biopsies (3x4 mm, 5-20 mg) were taken from the bladder body (2 cm cephalad from the left ureteric orifice) and also from the central trigone. Biopsies were collected into RNALater in the operating theatre, biopsies were dissected into mucosa (urothelium + lamina propria) and muscle and RNA was extracted [2]. Mucosal biopsies were evaluated for TRPV1 mRNA expression using quantitative competitive RT-PCR (QC-RT-PCR) [2]. TRPV1 data were normalised for expression of β-actin in the same tissue. Collection of human bladder specimens was approved by local ethics committee (HREC 03175).

Results

Table 1. TRPV1 mRNA ($\times 10^5$ copies /μg total RNA) expressed in human bladder biopsies

	Control	PBS	IDO
Body mucosa	14.2 (8.2-20.7) n = 35	8.2 (4.2-20.3) n = 17	11.4 (6.7-16.1) n = 10
Trigonal mucosa	4.1 (0.77-26.2) n = 6	17.5 (10.9-28.0) * n = 20	10.9 (8.5-15.7) n = 12

*p < 0.05 compared to trigonal mucosa of control biopsies (Kruskal-Wallis nonparametric one way ANOVA test followed by Dunn's multiple comparison). Data are median (IQR).

No age-related differences in TRPV1 mRNA were seen in control samples from body mucosa (n = 35, r^2 = 0.025, *P* = 0.36), trigonal mucosa (n = 6, r^2 = 0.025, *P* = 0.76), or detrusor muscle (n = 12, r^2 = 0.11, *P* = 0.33). The expression of TRPV1 mRNA from PBS trigonal mucosa was significantly higher than in control trigonal mucosa (Table 1). No difference was seen in expression in IDO trigonal mucosa compared with control (Table 1).

The expression of TRPV1 mRNA from PBS trigonal mucosa was significantly higher than in PBS bladder body mucosa (n = 16, Fig 1a). In contrast, in patients with IDO there was no difference between trigonal mucosa and body mucosa (n = 10, Fig 1b).

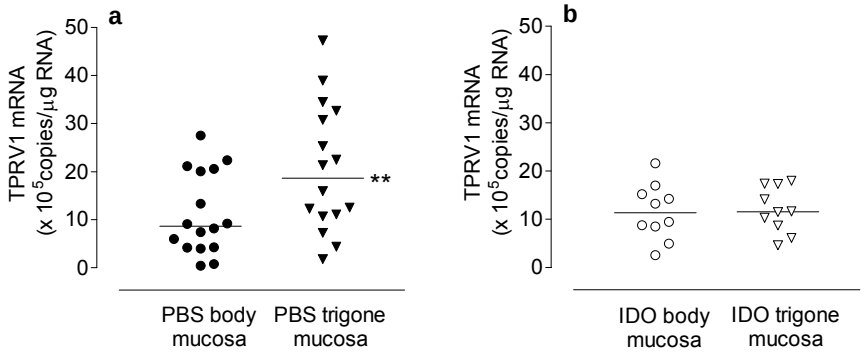

Fig 1. QC-RT-PCR determination of TRPV1 mRNA expression in biopsies from (**a**) PBS and (**b**) IDO patients.

One of the most interesting finding from this study was that there was a significant inverse correlation between TRPV1 expression in trigonal mucosa with the volume at first sensation of filling during cystometry (Fig 2a) in PBS patients. This relationship between TRPV1 mRNA expression and urodynamic findings was not seen in IDO patients (Fig 2b).

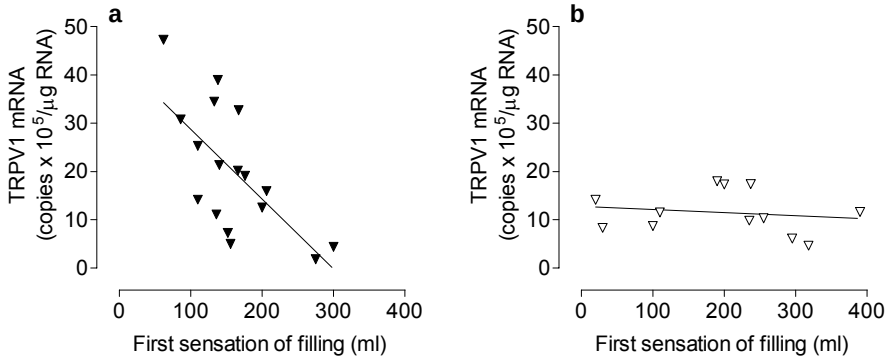

Fig 2. The TRPV1 mRNA expression level in trigonal mucosa of PBS patients was correlated inversely with the bladder volume at first sensation of bladder filling (**a**, r^2 = 0.45, *P* = 0.003). There was no correlation between TRPV1 mRNA expression in trigonal mucosa and bladder volume at first sensation in IDO patients (**b**, r^2 = 0.027 *P* = 0.61).

Interpretation of results

Our study suggests that the symptoms of PBS were associated with the increased expression of TRPV1 mRNA in the trigonal mucosa, whereas no such increase was seen in IDO. At cystoscopy, inflammatory and pseudomembranous changes are commonly seen in trigonal epithelium of women with PBS. Urological opinion is divided as to the relationship between the cystoscopic appearance and the symptomatology. Increased signaling from the trigone is thought to relate to urgency in a variety of conditions. Thus TRPV1 expression levels in the trigonal mucosa may relate to the strength of the afferent nerve signaling, and the sensation of urgency. The urgency experienced by women with IDO may result from a different mechanism.

Concluding message

Our study has provided scientific evidence that there is a distinctly different molecular basis between PBS and IDO. This may provide evidence-based justification for re-defining the type of urgency experienced by people who show stable cystometry and inflammation lesions within the bladder. Recently this issue has been addressed: “a strong case can be made for suggesting that the definition of urgency should be further qualified by adding the phrase ‘for fear of leakage’, which was previously in the definition but abandoned at the time of the last revision of terminology” [3].

References

1. Proc Natl Acad Sci USA (2001) 98:13396-401
2. Br J Pharmacol (2005) 114: 1089-1099
3. BJU Int (2006) 95: 274-275

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