Expression of 5-Hydroxytrptamine Receptors in Human Urinary Bladders with Benign Prostatic Hyperplasia

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ABSTRACT

Introduction: This study investigated the mRNA expression pattern and distribution of 5-hydroxytryptamine (5-HT) receptors 5-HT_{2A}, 5-HT_{2B}, 5-HT_{3A}, 5-HT_4, and 5-HT_7 within the urothelium and detrusor of normal bladder tissue and in the urothelium of bladders from patients with benign prostatic hyperplasia (BPH).

Methods: Normal urinary bladder specimens were obtained from 13 patients undergoing radical cystectomy due to bladder cancer (normal group) and BPH specimens were obtained from 27 benign prostatic obstruction patients receiving transurethral prostatectomy or retropubic prostatectomy. Receptor subtype mRNA expression was determined by real-time reverse transcription polymerase chain reaction on urothelium, detrusor, and whole mucosal preparations. Receptor distribution was determined by immunohistochemistry.

Results: In normal tissues, expressions of 5-HT_{2B} and 5-HT_7 receptor mRNAs in the urothelium, detrusor, and whole mucosa were greater than the average expression for all receptor subtype mRNAs. 5-HT_{2B} receptor protein was distributed in the apical urothelium and among the detrusor smooth muscle layers. In contrast, the 5-HT_7

receptors were within the urothelium middle cell layers and detrusor smooth muscle cells. The expression pattern of each 5-HT receptor subtype mRNA within the BPH urothelium was similar to that in the normal urothelium. The expression level of 5-HT_{2A} receptor mRNA in the BPH group was significantly lower than the normal group; however, the expression of both 5-HT_{3A} and 5-HT_7 mRNAs were significantly higher. The expression of both 5-HT_{2B} and 5-HT_4 mRNAs were not significantly different between the normal and BPH groups.

Conclusion: In normal urinary bladders, the expressions of both 5-HT_{2B} and 5-HT_7 mRNAs were higher compared to the 5-HT_{2A}, 5-HT_{3A}, and 5-HT_{3A} mRNAs. The distributions of 5-HT_{2B} and 5-HT_7 receptors were different in the urothelium and detrusor layers. The 5-HT_{3A} and 5-HT_7 receptor mRNAs in the BPH group were significantly higher compared to the normal urothelium, while the 5-HT_{2A} mRNA was significantly lower.

Keywords:

5-hydroxytriptamine receptor, urinary bladder, urothelium, detrusor, human

INTRODUCTION

The neurotransmitter 5-hydroxytryptamine (5-HT) is an important regulator of the micturition reflex and urinary continence in the lower urinary tract, as well as central nervous system [1-3]. 5-HT receptors are classified into seven subtypes (5-HT_{1-7}), which are further divided into 14 structural and pharmacological 5-HT receptor subtypes [4, 5]. In the human urinary bladder, the existence of 5-HT receptor subtypes has been suggested by electrical field stimulation and/or pharmacological analysis. Activation of the 5-HT_2 receptor produces contractions of the detrusor [6], and the 5-HT_1, 5-HT_2, and 5-HT_3 receptors facilitate cholinergic transmission [7]. Other studies showed detrusor contractions through activation of the 5-HT_4 receptors induced by electrical field stimulation [8] and the receptor agonist [9]. The 5-HT_7 receptors have been demonstrated pharmacologically in human detrusor [10]. Additionally, the existence of 5-HT_{2A} and 5-HT_{2B} receptors [11, 12], 5-HT_{3A} receptors [13], 5-HT_4 receptors [14, 15], and 5-HT_7 receptors [16-20] in several animals has been demonstrated with similar methods. However, in the human urothelium and detrusor layers, the mRNA expression levels and the distributions of these 5-HT receptor

subtypes have not been well investigated.

To demonstrate the expression patterns of 5-HT receptor subtypes, we semi-quantitatively estimated the levels of 5-HT_{2A}, 5-HT_{2B}, 5-HT_{3A}, 5-HT_4, and 5-HT_7 mRNAs within the mucosa of the bladder wall and separately within the urothelium and the detrusor. Based on the mRNA expression levels, we then determined by immunohistochemistry the distribution of the most highly expressed 5-HT receptor subtypes. In addition, we determined if the mRNA expression levels of the 5-HT receptor subtypes within the urothelium of patients with benign prostatic hyperplasia (BPH) were different from the normal urothelium.

METHODS

Patients

This study was performed with the approval of the Ethics Committee of Shinshu University School of Medicine. After the aims of the study were explained, each patient provided informed consent to participate. By providing this consent, each BPH patient agreed to allow the urethelial biopsy necessary for this study. All patients were treated in accordance with the Declaration of Helsinki.

At Shinshu University Hospital, normal urinary bladder specimens were obtained from 13 patients (9 males, 4 females, mean age 68.8 years) undergoing radical cystectomy due to bladder cancer from July 2012 to April 2014. The specimens were harvested from a region apart from the bladder tumor and designated the normal group.

Patients diagnosed with benign prostatic hyperplasia at Shinshu University Hospital from October 2006 to May 2011 were enrolled in this study (mean age 72.1 years). The urothelium specimens, designated the BPH group, were obtained from the mucosa of the posterior bladder wall during transurethral prostatectomy (TURP, n=20) or retropubic prostatectomy (n=7) by means of transurethral cold punch biopsy.

Real-time reverse transcription polymerase chain reaction (RT-PCR)

Without the use of any magnification, the normal urinary bladder mucosa was separated into the urothelium and detrusor components. Whole mucosas and the separated urothelia and detrusors were homogenized separately, and total RNA was extracted from each with the RNeasy Mini Kit (Qiagen Inc., Valencia, CA, USA). Complementary DNA (cDNA) was synthesized from 0.1 μg of total RNA with the High-Capacity cDNA Archive Kit (Applied Biosystems, Foster City, CA, USA). The synthesized cDNA was mixed with the following gene assay probes (Applied Biosystems): 5-HT_{2A} receptor (Hs01033524_m1), 5-HT_{2B} receptor (Hs00168362_m1), 5-HT_{3A} receptor (Hs00168375_m1), 5-HT_{4} receptor (Hs00410577_m1), 5-HT_{7} receptor (Hs04194798_s1), or eukaryotic 18S rRNA (Hs99999901_s1), which was used as the internal standard. Real-time RT-PCR of the cDNA-probe mixed solution was performed at 50ºC for 2 min followed by 95ºC for 10 min. These were followed by 40 cycles at 95ºC for 15 sec and 60ºC for 1 min. Relative gene expression levels were calculated by the delta-delta method as the ratio to threshold cycle (Ct) value of the internal standard

gene 18S rRNA. Real time RT-PCR of the BPH group urothelium was also performed. mRNAs with Ct values over 35 were considered as undetectable.

Immunohistochemistry

The trimmed normal urinary bladder specimens were fixed with 4% paraformaldehyde and 4% sucrose in 0.1 M phosphate buffer, pH 7.4, for 12 hr at 4˚C. The treated samples were embedded in paraffin and cut in 5-μm thick serial sections. The sections were deparaffinized, rehydrated, and rinsed with phosphate buffered saline (PBS), and then immersed in 10 mM sodium citrate, pH 6.0. For antigen retrieval, the sections were microwaved at 100˚C for 5 min. The specimens were coated with 1.5% normal donkey serum (Chemicon International Inc., Temecula, CA, USA) and 1.5% non-fat milk in PBS for 1 hr at 4˚C. Following rinsing, triple staining of each section was achieved by incubation with either 5-HT_{2B} receptor antibody (1:100, rabbit polyclonal, HPA012867, Atlas Antibodies AB, Stockholm, Sweden) or 5-HT_7 receptor antibody (1:100, rabbit monoclonal, LS-A6673, Lifespan Biosciences, Inc., Seattle, WA, USA), and both uroplakin III antibody (UP III, 1:100, goat polyclonal, sc-15186, Santa

Cruz Biotechnology Inc., Santa Cruz, CA, USA) and smooth muscle actin antibody (SMA, 1:100, mouse monoclonal, 61001, Progen Biotechnik GmbH, Heidelberg, Germany) for 12 hr at 4ºC. The sections were rinsed with PBS, and then incubated with donkey anti-rabbit IgG secondary antibody conjugated with Alexa Fluor 488 (1:250, Life Technology Co.) for 1 hr at 4ºC and donkey anti-goat and anti-mouse IgG secondary antibody conjugated with Alexa Fluor 594 (1:250, Life Technology Co.) for 12 hr at 4ºC. Finally, after rinsing, cell nuclei were counterstained with 5 μg/ml 4', 6-diamidino-2-phenylindole dihydrochloride (DAPI, Life Technology Co.). The stained samples were observed with a Leica DAS Microscopethe (Leica Microsystems GmbH, Wetzlar, Germany).

Statistical Analysis

Results were expressed as means ± standard error. Statistical differences were determined using the Excel® Statistics program (Esumi Co., Ltd. Tokyo, Japan). Comparisons were made by Mann-Whitney U test. P-values less than 0.05 were considered statistically significant. Effect sizes were calculated by using G*Power

version 3.0.10 (Heinrrich Heine Universität Düsseldorf, Germany).

RESULTS

Expression Patterns of 5-Hydroxytryptamine Receptor Subtypes in Normal Urinary Bladders

To investigate expression patterns of the 5-HT receptor subtype mRNAs, the expression of each subtype mRNA was calculated relative to the averaged expression of all of the subtype mRNAs (Fig. 1). In the urothelial layers, expression of 5-HT_{2B} and 5-HT_7 receptor mRNAs was greater than the other receptor subtype mRNAs (Fig. 1A). For 5-HT_{2B}, the relative expression level was 7.98±2.08, and for 5-HT_7, the relative expression level was 2.44±0.64. The relative mRNA expression of 5-HT_{2A}, 1.46±0.37, was similar to that for all subtypes (Fig. 1A). In contrast, the relative mRNA expressions for receptor subtypes 5-HT_{3A} and 5-HT_4, 0.34±0.11 and 0.50±0.19 respectively, were lower than the other subtypes (Fig. 1A). Within the detrusor layers, the relative mRNA expressions for receptor subtypes 5-HT_{2B} and 5-HT_7 were also greater than the other subtype mRNAs by 7.28±3.97 and 4.77±3.06 respectively (Fig. 1B). For the mucosa specimens of normal bladder tissue, which included the urothelium and detrusor, the relative expressions for 5-HT_{2B} and 5-HT_7 receptor mRNAs were

5.32±2.25 and 3.83±1.65 (Fig. 1C); however for 5-HT_{2A}, 5-HT_{3A}, and 5-HT_4 receptors, the relative mRNA expressions were 0.93±0.33, 0.79±0.35, and 0.35±0.08 respectively.

In preliminary immunohistochemical studies, the presence of both 5-HT_{2B} and 5-HT_7 receptors within the urothelial and detrusor layers were showed (Fig. 2). In the urothelium, the 5-HT_{2B} receptors were present within the most apical one or two cell layers, nearest the lumen (Fig. 2A). The 5-HT_7 receptors were detected within the middle layers of the urothelium (Fig. 2B). The 5-HT_{2B} receptors were expressed among the smooth muscle layers in the detrusor (Fig. 2C), and the 5-HT_7 receptors were expressed within the smooth muscle cells and within the interstitial spaces of these layers (Fig. 2D).

Expression of 5-Hydroxytrptamine Receptor mRNAs in the Urothelium of Benign Prostatic Hyperplasia Patients

The relative expression level of each 5-HT receptor subtype mRNA within the urothelium of patients in the BPH group was also determined. As in the normal tissue samples, expressions of both 5-HT_{2B} and 5-HT_7 receptor mRNAs were greater than the

other receptor subtype mRNAs (Fig. 3). The relative expression levels of 5-HT_{2B} and 5-HT_7 were 7.76±0.76 and 3.33±0.32, respectively. For receptor subtypes 5-HT_{2A}, 5-HT_{3A}, and 5-HT_4, the relative expression levels were 0.71±0.13, 0.44±0.09, and 0.43±0.06, respectively.

For each receptor subtype, the expression levels of mRNAs within the urothelia of the normal and BPH groups were calculated relative to the averaged expression of both groups (Table 1). Compared to the normal group, the relative expression level of 5-HT_{2A} mRNA within the urothelium in the BPH group was significantly lower ($P<0.05$, effect size d=0.91); however, the relative expression level of 5-HT_{3A} mRNA was significantly higher ($P<0.05$, effect size d=0.53). The relative expression level of 5-HT_4 mRNA in the BPH group was not significantly different from the normal tissue (effect size d=0.16). While the relative expression levels of 5-HT_{2B} mRNA in the urothelia of the normal and BPH groups were high (Figs. 1A, 3), there was no significant difference between the groups (effect size d=0.21). The relative expression levels of 5-HT_7 in the urothelia of both groups were also higher than the average for all subtype mRNAs (Figs. 1A, 3); however in contrast to 5-HT_{2B}, expression in the BPH group was significantly

greater than in the normal group ($P<0.01$, effect size $d=0.95$).

DISCUSSION

This study documented the presence of 5-HT receptor subtypes expressed within normal urinary bladder tissues taken from patients with bladder cancer and from patients with BPH. In normal urinary bladders, the expression of both 5-HT_{2B} and 5-HT_7 mRNAs were higher compared to the 5-HT_{2A}, 5-HT_{3A}, and 5-HT_{3A} mRNAs. This expression pattern was found in both the urothelium and detrusor layers. Thus, we analyzed the immunohistochemical distributions of 5-HT_{2B} and 5-HT_7 receptors within these tissues. The 5-HT_{2B} receptors were present in the apical one or two cell layers of the urothelium and among the smooth muscle layers in the detrusor. In contrast, the 5-HT_7 receptors were expressed in the middle layers of the urothelium and within the smooth muscle cells in the detrusor.

In the urothelium of the BPH patients, the expression patterns of 5-HT receptor mRNAs were similar to those of the normal urothelium. Both 5-HT_{2B} and 5-HT_7 mRNAs were higher compared to the other subtype mRNAs. The expression levels of 5-HT_{2B} and 5-HT_4 receptor mRNAs were not significantly different between the normal and BPH group. The 5-HT_{2A} mRNA within the urothelium of BPH group was

significantly lower than that of the normal group; however, both 5-HT_{3A} and 5-HT_7 receptor mRNAs in the BPH group were significantly higher compared to the normal urothelium.

Ketanserin, a 5-HT_{2A} receptor agonist, increased maximum and mean urinary flow rates, and decreased urethral pressure profile measurements without serious side-effects in male patients with prostatism [21]. In rats with streptozotocin-induced diabetes mellitus, the 5-HT_{2A} receptor antagonist sarpogrelate hydrochloride inhibited 5-HT-induced detrusor contractions [22]. Furthermore, the alpha-1 adrenoceptor antagonist naftopidil, which was demonstrated a high affinity to the 5-HT receptors as same as the alpha-1 adrenergic receptors, inhibited bladder contractions through 5-HT_{2A} and 5-HT_{2B} receptors in rats with bladder outlet obstruction [23, 24]. These studies and our own results suggest that regulation of 5-HT receptors might provide promising clinical treatments for lower urinary tract symptoms.

In the present study, we did not attempt to examine any potential excitatory effects by either 5-HT_{2B} or 5-HT_7 receptor agonists; nor did we look for inhibitory effects using these receptor antagonists in human bladder strips. We also did not investigate any

potential relationships between bladder functions measured by video urodynamic studies in BPH patient and the higher mRNA expression level of 5-HT_{3A} and 5-HT_7 within the urothelium. While this study had these limitations, we successfully showed the characteristics of 5-HT receptor subtype expression within the human urinary bladder.

CONCLUSION

In normal urinary bladders, the expression of both 5-HT_{2B} and 5-HT_7 mRNAs within the whole mucosa were higher compared to the 5-HT_{2A}, 5-HT_{3A}, and 5-HT_4 mRNAs. The separate urothelium and detrusor layers showed similar expression patterns. The 5-HT_{2B} receptor proteins were present in the most apical cells of the urothelium and among the smooth muscle layers in the detrusor. The 5-HT_7 receptors were present in the middle layers of the urothelium and within the smooth muscle cells in the detrusor. In the urothelium of the BPH patients, the expression pattern of 5-HT receptor mRNAs was similar to the normal urothelium. The expression levels of 5-HT_{2B} and 5-HT_4 mRNA were not significantly different between the two groups. The expression of 5-HT_{2A} mRNA was significantly lower in the BPH group while expressions of 5-HT_{3A} and 5-HT_7 mRNAs were significantly higher.

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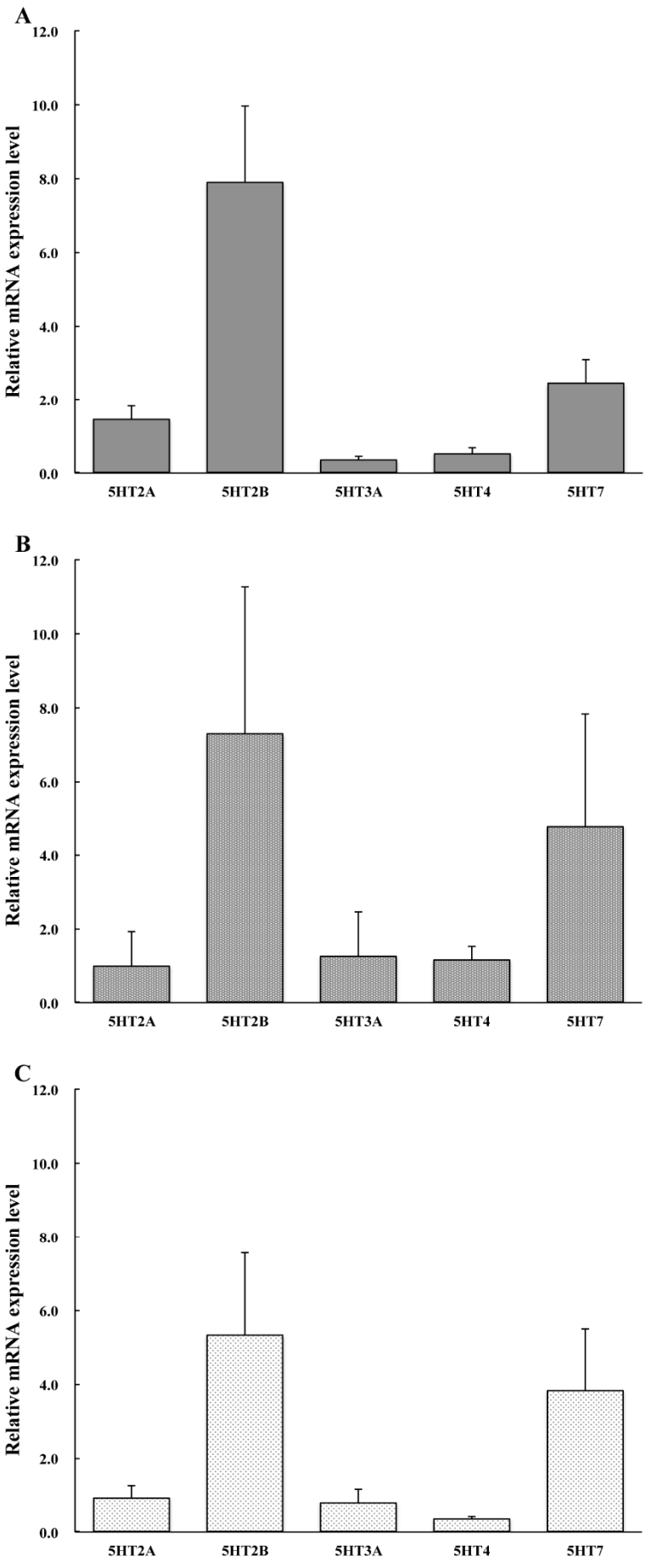
Figure Legends

Figure 1. Relative expressions of 5-hydroxytryptamine receptor subtypes within normal urinary bladders. In the urothelium (A), detrusor (B), and whole mucosa (C), the expression of both 5-HT_{2B} and 5-HT_7 mRNAs were over 2-fold greater than the average of all receptor subtype mRNAs. The threshold cycle (Ct) values of 5-HT_{3A} receptor mRNA in 2 patients were undetectable in each layer.

Figure 2. Distribution of 5-hydroxytrptamine 2B and 7 receptors within the normal urothelium and detrusor. (A and B) The 5-HT_{2B} (green, arrows) and 5-HT_7 (green, arrowheads) receptors were present within the most apical 1 or 2 cell layers. (C) The 5-HT_{2B} receptors (green, arrows) were expressed among the muscle layers (red). (D) The 5-HT_7 receptors (green, arrowheads) were present within the smooth muscle cells (red). Blue, nuclei; bar = 20 μm.

Figure 3. Relative expression of 5-hydroxytryptamine receptor subtypes within the urothelium of benign prostatic hyperplasia patients. The expression pattern of the 5-HT

receptor subtypes was similar to that in the normal whole mucosa. Ct values of 5-HT_{3A} receptor mRNA in 2 patients were undetectable.


A
B
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Relative mRNA expression level
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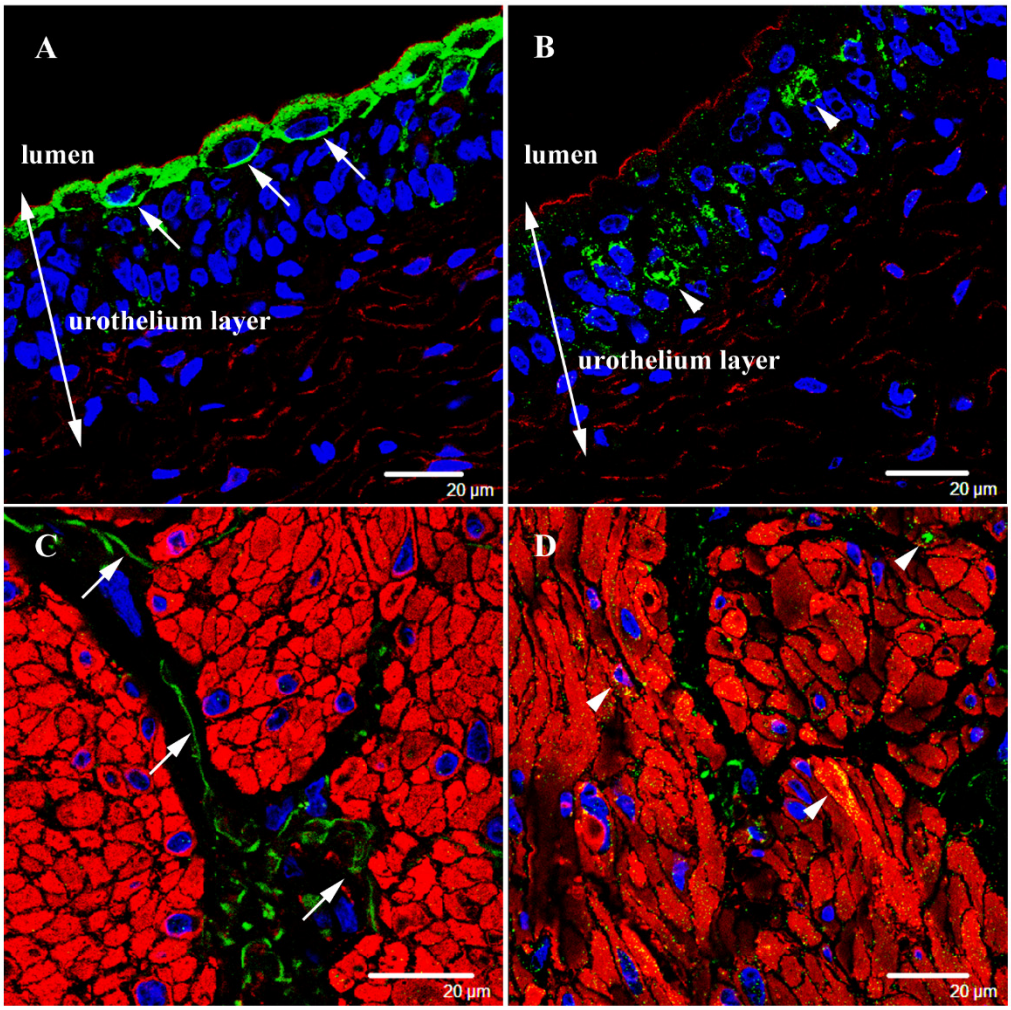
5HT2A
5HT2B
5HT3A
5HT4
5HT7

Figure 1


A
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urothelium layer
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C
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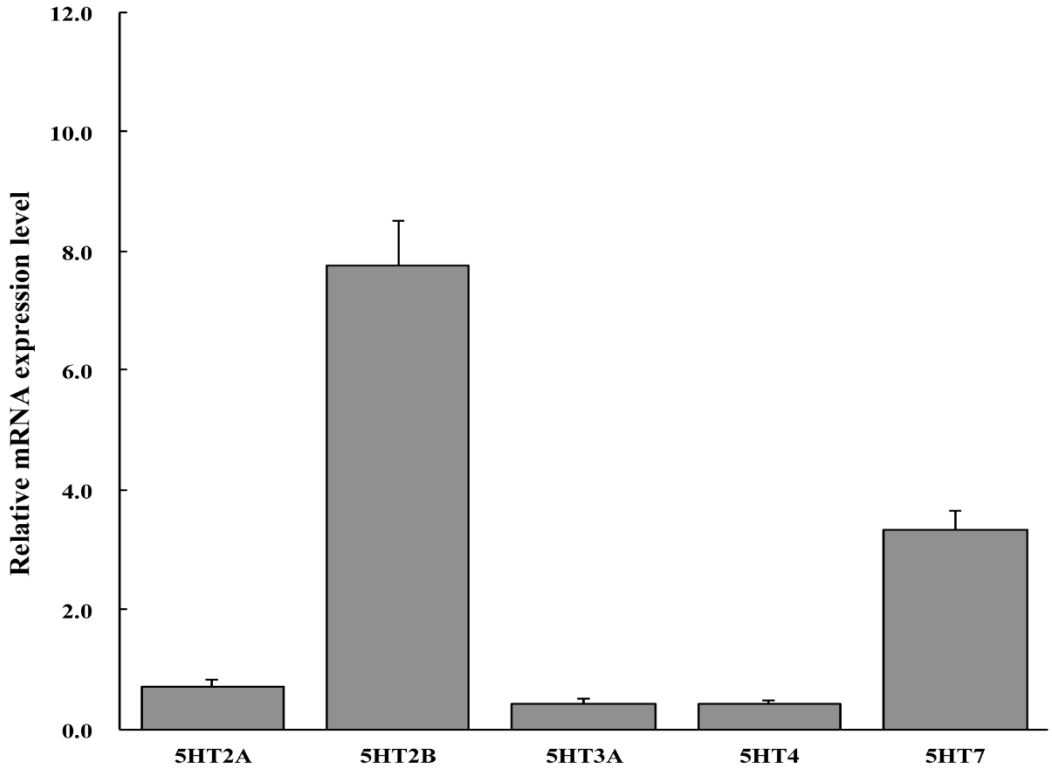
Figure 2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Relative mRNA expression level
5HT2A
5HT2B
5HT3A
5HT4
5HT7

Figure 3

Table 1. Comparison of urothelial 5-hydroxytrptamine receptor subtype mRNA relative expression levels

	5-HT_{2A}	5-HT_{2B}	5-HT_{3A}	5-HT_{4}	5-HT_{7}
Normal	2.68±0.67	1.36±0.36	0.98±0.18	1.23±0.36	0.79±0.10
BPH	1.15±0.21*	1.17±0.11	1.60±0.32*	1.40±0.20	1.26±0.12**

5-HT: 5-hydroxytrptamine. Ct values of 5-HT_{3A} receptor mRNA in two patients were undetected in each group. *P<0.05, **P<0.01; compared with normal group (Mann-Whitney U test).