INTERNATIONAL JOURNAL OF UROLOGY

International Journal of Urology (2012) 19, 86–89 doi: 10.1111/j.1442-2042.2011.02883.x

Short Communication

Admissions related to interstitial cystitis in Japan: An estimation based on the Japanese Diagnosis Procedure Combination database

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Abbreviations & Acronyms
IC = Interstitial cystitis
DPC = Diagnosis Procedure Combination
JUA = Japanese Urological Association

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Received 21 May 2011; accepted 27 September 2011. Online publication 1 November 2011

Abstract: We estimated the incidence of admissions related to interstitial cystitis in Japan using a national administrative claims database, the Diagnosis Procedure Combination database, which included information for 53.6% of urological training hospitals certified by the Japanese Urological Association. "Admissions related to interstitial cystitis" was defined as those cases whose ICD-10 code for the main reason for admission was N301 (interstitial cystitis) between 2007 and 2009. Among 8.42 million inpatient cases, 784 female and 212 male patients with interstitial cystitis were identified. The ratio of females to males was 3.69 and the median age was 67 years (range 5–92 years). The admission incidence (per 100 000 person-years) in females and males was estimated to be 1.35 (95% confidence interval 1.25–1.46) and 0.37 (0.31–0.42), respectively. This incidence is low compared with other reports. Possible reasons for this finding include racial difference, clinical examination methods, lack of outpatient data and poor health-care coverage of interstitial cystitis.

Key words: bladder, epidemiology, incidence, interstitial cystitis, Japan.

Introduction

Interstitial cystitis (IC) is a chronic disease of the urinary bladder characterized by lower urinary tract symptoms, such as urinary frequency, bladder hypersensitivity and/or bladder pain and resultant serious impairment of quality of life.[1]

Although the National Institute of Arthritis, Diabetes, Digestive and Kidney Disease proposed the diagnostic criteria of IC for research use in 1988,[2] it has not been widely used in the clinical setting because of its strictness and complicacy. To promote research activity and medical care of IC in Japan and East Asia, the Clinical Guidelines for IC were established by the Society of Interstitial Cystitis of Japan in 2007.[1]

Estimation of the incidence or prevalence of IC in the general population is difficult because of its rarity. Although several articles estimating the incidence or prevalence of IC have been published,[3–10] many of them were based on restricted sample populations (i.e. office visitors and nurses' cohort) or scoring questionnaire research and few focused on male patients. To our knowledge, just three articles from the USA have been published to estimate the male and female incidence or prevalence of IC in the general population based on clinical diagnosis.[5,9,10]

The present study evaluated the incidence of admissions related to IC in both the male and female general population in Japan, using the Diagnosis Procedure Combination (DPC) database, which is a nationwide administrative database.

Methods

The DPC database

The DPC database is a case-mix inpatient claims database.[11–14] During our study period of 2007–2009, the database contains annually approximately 2.6 million inpatient cases from approximately 850 hospitals from July to December (6 months per each year), which represents approximately 44% of all acute care inpatient hospitalizations in Japan. Given the anonymous nature of the data collection process, informed consent was not required. Study approval was obtained from the Institutional Review Board in the University of Occupational and Environmental Health.

Japanese Urological Association-certified hospitals

The Japanese Urological Association (JUA) is the professional urological association in Japan. The JUA certifies urological specialists and hospitals where the teaching system is ensured (JUA-certified hospitals).

Study samples

In the DPC database, one disease should be assigned to "the main reason for admission" category. We defined "admissions related to IC" as those cases whose ICD-10 code for the main reason for admission was N301 (IC), and we identified them from the DPC database in 2007–2009.

Estimation of prevalence of IC

We estimated the incidence of admissions related to IC based on stratified hospital bed volume. First, we collected the number of beds in all JUA-certified hospitals and hospitals that had joined the DPC database. Hospitals were stratified with bed volume categories. The estimated annual number of IC cases (Yi) and the 95% confidence intervals (CI) were calculated with the following equation using Wald confidence intervals for the population proportion:[13]

$$Yi/Ni = pi \pm Z\sqrt{pi(1-pi)/(ni \times 1.5)}$$

where Ni is the number of beds in all JUA-certified hospitals, ni is the number of beds in JUA-certified hospitals that joined the DPC database, $pi = Xi/(ni \times 1.5)$ (Xi is the observed number of IC cases in JUA-certified hospitals that joined the DPC database between July and December, 2007–2009), and $Z = 1.96$.

Results

Among 8.42 million inpatients in the study population, we identified 996 admissions related to IC (Table 1). The ratio of females to males was 3.69 and the median age was 67 years (range 5–92 years). Almost all patients (95.3%) were hospitalized in JUA-certified hospitals. A vast majority of patients underwent cystoscopic intervention. Although they were minor, cystectomies and augmentation cystoplasties were also selected for therapy.

Table 1 Distribution of male and female interstitial cystitis patients from the Diagnosis Procedure Combination database

Total	Males	Females
	212 (100.0%)	784 (100.0%)
Age (years)		
≤19	4 (1.9%)	9 (1.1%)
20–29	5 (2.4%)	29 (3.7%)
30–39	7 (3.3%)	42 (5.4%)
40–49	9 (4.2%)	47 (6.0%)
50–59	26 (12.3%)	95 (12.1%)
60–69	65 (30.7%)	215 (27.4%)
70–79	75 (35.4%)	268 (34.2%)
80–89	20 (9.4%)	76 (9.7%)
≥90	1 (0.5%)	3 (0.4%)
Median (IQR)	67 (59–76)	67 (57–74)
Year		
2007	80 (37.7%)	263 (33.5%)
2008	58 (27.4%)	242 (30.9%)
2009	74 (34.9%)	279 (35.6%)
JUA hospital	200 (94.3%)	750 (95.7%)
Intervention		
Cystoscopic interventions including hydrodistension	176 (83.0%)	706 (90.1%)
Augmentation cystoplasty	2 (0.9%)	2 (0.3%)
Simple cystectomy	1 (0.5%)	2 (0.3%)
Implantation of spinal cord stimulation apparatus	3 (1.4%)	1 (0.1%)
Missing or others	30 (14.2%)	73 (9.2%)

IQR, interquartile range; JUA, Japanese Urological Association.

Table 2 shows the distribution of hospitals and IC cases stratified with bed volume categories. Overall, the DPC database covered 53.6% of JUA-certified hospitals and 63.4% of those beds. The estimated annual number of IC cases per year was 886 in females and 231 in males. According to the Population Census Data, the population of Japan in 2008 was approximately 65.44 million females and 62.25 million males; therefore, the incidence of admission related to IC (per 100 000 person-years) in females and males was estimated as 1.35 (95% CI 1.25–1.46) and 0.37 (0.31–0.42), respectively.

Table 2 Estimated incidence of admissions related to interstitial cystitis in Japan

Bed volume	JUA-certified hospitals (2007–2009)		JUA-certified hospitals that joined the DPC database (2007–2009)				No. IC patients in the DPC database for 1.5 years [*Xi*]†		Estimated annual no. IC patients (95% confidence interval) [*Yi*]‡	
	n	No. of beds [*Ni*]	*n*		No. of beds [*ni*]		Males	Females	Males	Females
≥800	62	60 768	50	80.6%	50 278	82.7%	42	183	34 (24–44)	147 (126–169)
600–799	107	72 437	80	74.8%	54 394	75.1%	31	115	28 (18–37)	102 (83–121)
400–599	336	161 951	224	66.7%	109 834	67.8%	41	165	40 (28–53)	162 (137–187)
200–399	512	153 265	269	52.5%	81 480	53.2%	94	273	118 (94–142)	342 (302–383)
≤199	231	30 486	46	19.9%	7406	24.3%	4	48	11 (0–22)	132 (95–169)
Total	1248	478 907	669	53.6%	303 392	63.4%	212	784	231 (198–263)¶	886 (819–952)¶
Total population in 2008 (100 000 persons)									622.5	654.4
Incidence (per 100 000 person-years)									0.37 (0.31–0.42)	1.35 (1.25–1.46)

†Data were collected from six months (July to December) of each 3 years (2007–2009). ‡$Yi/Ni = pi \pm 1.96 \times \sigma i$, where $pi = Xi/(ni \times 1.5)$, $\sigma^2 = pi\,(1 - pi)/(ni \times 1.5)$. ¶$\Sigma Yi = \Sigma (Ni \times pi) \pm 1.96 \times (\Sigma Ni \times \sigma i^2)^{0.5}$. DPC, Diagnosis Procedure Combination; IC, interstitial cystitis; JUA, Japanese Urological Association.

Discussion

In the present study, we used a large administrative database and identified IC with a registered ICD-10 code. A similar method was used in two previous studies using Kaiser Permanente Northwest, a health maintenance organization in Portland, Oregon, USA. Clemens *et al.*[9] reported that "the prevalence" of IC during 1998–2002 was 197 and 41 per 100 000 in females and males, respectively, when IC was defined as the ICD-9 code 595.1, and Patel *et al.*[5] reported that "the incidence" of IC during 2002–2005 was 15 per 100 000 in females (no male patients were identified). Therefore, there is a 10-fold discrepancy between our results and those of Patel *et al.*

The incidence of IC varies widely, even though IC is diagnosed by clinical examination. Robert *et al.* analyzed Olmsted Country cohort data (1976–1996) and reported that the incidence of IC diagnosed through cystoscopic intervention was 1.6 and 0.6 per 100 000 in females and males, respectively.[10] Leppilahti *et al.* carried out a clinical examination in Finnish people who scored high points in the O'Leary-Sant IC symptom and problem index (OLS) questionnaire, and concluded that the prevalence of probable IC in women was 230 per 100 000 and that of possible/probable IC was 530 per 100 000.[8]

Recently, several questionnaires measuring the severity of IC, such as the OLS, have been developed. According to some OLS-based surveys, the prevalence of possible IC or painful bladder syndrome (per 100 000 females) is estimated to be 575 in the USA,[7] 306 in Austria,[6] 265 in Japan[4] and 261 in Korea.[3] These data suggest that there is some racial discrepancy between Asia, European countries and the USA, but the differences seem not so largely radical to solely explain the 10-fold gap. This implies that several IC patients remain undiagnosed and untreated in Japan.

Although the Clinical Guidelines for IC were released in January 2007 in Japan to promote research and clinical activity for IC,[1] the number of patients did not increase (Table 1). We consider there to be two possible reasons for this finding. First, racial variants and differences in database background could be attributed to our low IC incidence. In particular, the DPC database did not contain outpatient cases and our result of "incidence of admission related to IC" did not directly represent overall IC incidence. A previous report described that hydrodistension can be safely carried out under local anesthesia without hospitalization.[15] Second, Japanese national health-care insurance does not currently cover hydrodistension. Special approval from authorities is required to carry out hydrodistension (this restriction was lifted in April 2010).

Finally, we showed that the DPC database is highly represented in the urological field. The database coverage rate is approximately 35% of whole acute care beds,[13] but by restriction to JUA-certified hospitals, it increased to 53.6%. This high coverage enables accurate clinical assessment.

There are several limitations in the present study. First, the definition of IC was only based on an ICD-10 code in the administrative database. Neither chart reviews nor scoring questionnaires were available in the database. Second, because the present study was based on administrative claims data, the validity and reliability of the written diagnoses were limited, resulting in underestimation.

The incidence of admission related to IC from the DPC database (per 100 000 person-years) is estimated as 1.35 in

females and 0.37 in males. Possible reasons for this low incidence include racial difference, clinical examination methods, lack of outpatient data and poor health-care coverage for IC.

Acknowledgment

The present study was funded by a Grant-in-Aid for Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare, Japan (Grant number: H19-Policy-001).

Conflict of interest

None declared.

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間質性膀胱炎

膜の観察、最終診断を行います。

すなわち、間質性膀胱炎の診断は患者の症状・経過と検査所見を総合的に診ながら判断していく必要があるといえます。

ただ、診断基準がないため、現時点では原因不明の頻尿や膀胱痛を訴えている症例を診たら専門の施設に紹介するのが無難といえるかもしれません。

間質性膀胱炎とは

間質性膀胱炎は、1914年にHunnerによってはじめて報告された原因不明の膀胱の慢性炎症疾患で、頻尿・尿意亢進・尿意切迫感・膀胱痛・骨盤痛などを呈する疾患です。全例ではありませんが、疼痛を訴える場合、蓄尿に伴って痛みが悪化して、排尿で緩和することが多いです。

間質性膀胱炎の病因・病態は、いまだ不明であり、有効な治療法が見出されていないがために患者のQOLは症状により著しく障害されているのが現状です。また、その多彩な症状も相俟って診断基準が確立されておりません。それゆえ、間質性膀胱炎症状の発症から診断に至るまで、当科の間質性膀胱炎外来受診者で平均5.0年を要し、多くの患者が症状を訴えて泌尿器科をはじめ、内科、産婦人科、麻酔科（ペインクリニック）などを受診し、満足のいく治療が受けられず、結果としてドクターショッピングをしているのが現状です。

最近、間質性膀胱炎の中でもハンナー潰瘍という炎症に伴う粘膜糜爛を有するタイプと有さないタイプとでは病態が異なる可能性を示唆されており、今後更なる病因病態の解明、治療法の開発に繋がることが期待されています。

間質性膀胱炎の診断

確立された間質性膀胱炎の診断基準は存在しないのですが、わが国では日本間質性膀胱炎研究会発行の「間質性膀胱炎診療ガイドライン」に加え、"Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome (Homma Y, et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Int. J.Urol. 16: 597-615)"に準拠して診断、治療を行っております。それによると主に3つのポイントがあります。

❶患者の自覚症状：頻尿、尿意切迫感、膀胱痛、骨盤痛など

本疾患の特徴を一言で言えば、やはり膀胱痛です。疼痛を訴えない場合もあり、注意が必要ですが、蓄尿痛などの膀胱痛の訴えがある場合、間質性膀胱炎である可能性が高いです。

❷膀胱粘膜所見：膀胱拡張に伴う粘膜からの出血（点状出血、五月雨状出血）、潰瘍やそこからの滝状出血、潰瘍の治癒に伴う瘢痕、粘膜の引きつれなど

このような粘膜の変化は正常な膀胱粘膜では見られません。

❸除外診断：同様の症状を呈する尿路感染症、膀胱結石症、過活動膀胱、膀胱癌（特に上皮内癌）などの疾患の否定

とくにこの中で重要なのは悪性疾患（主に膀胱癌）の除外です。したがって、間質性膀胱炎を強く疑っても悪性疾患を完全に否定できない場合は、まずは膀胱水圧拡張術（後述）と膀胱粘膜生検を行うのは必須といえます。

診療の基本的なアルゴリズムは図1に示すとおりで、まずは自覚症状の聴取を行い、あわせて考えうる鑑別疾患の否定を行い、いよいよ間質性膀胱炎が疑わしい場合、膀胱水圧拡張術を行って膀胱粘

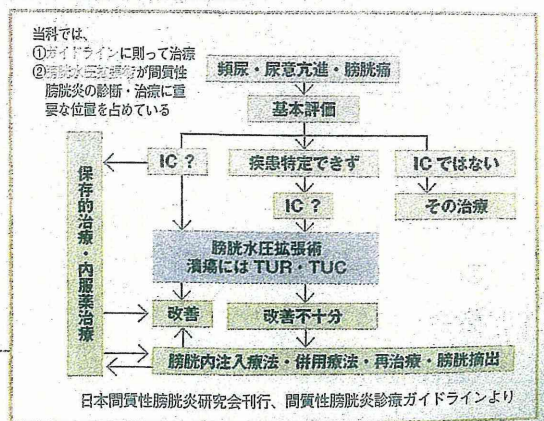
間質性膀胱炎の治療

現在、間質性膀胱炎の治療は2011年より保険適応となった膀胱水圧拡張術を中心として行うことが多いです。膀胱水圧拡張術は麻酔下で膀胱鏡下に膀胱内に生理食塩水を注入、内部を観察し、その後拡張、排水を行ってその間の粘膜の変化を観察します。間質性膀胱炎の場合、潰瘍や点状出血などの粘膜変化を認めることがほとんどです。本治療は、診断・治療を兼ねており、特に潰瘍を有する症例ではその切除・焼灼により疼痛の改善をもたらす場合が多く、本疾患の診断治療の要であるといえます。術後は、症状に応じて抗ヒスタミン薬、三環系抗うつ薬などの内服治療、DMSO（Dimethyl sulfoxide）、ヘパリンなどの膀胱内注入療法などを併用することが多いのですが、エビデンスが確立された治療は皆無に等しいのが現状で、多くの場合は個々の症例の状態に合わせて処方を調整しているのが現状です。

また、中には症状コントロール不良で膀胱摘出を行う症例も存在しますが、本疾患は良性疾患であるため、適応の選択には慎重を期すべきことは言うまでもありません。

参考：間質性膀胱炎診療ガイドライン

図1　診療の基本的な流れ



日本間質性膀胱炎研究会刊行、間質性膀胱炎診療ガイドラインより

TUR：経尿道的膀胱粘膜切除 TUC：経尿道的凝固術

間質性膀胱炎

頻尿・尿意亢進・尿意切迫感・膀胱痛・骨盤痛などの症状が見られる間質性膀胱炎。その診断方法について解説します。

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Ann Hematol (2012) 91:1505–1506
DOI 10.1007/s00277-012-1419-0

LETTER TO THE EDITOR

Primary MALT lymphoma of the urinary bladder in the background of interstitial cystitis

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Received: 17 January 2012 / Accepted: 23 January 2012 / Published online: 3 February 2012

Dear Editor,

Primary urinary bladder lymphoma is an extremely rare disease, and its frequency is identified as 0.2% of extranodal lymphomas [1]. Its dominant histology is mucosa-associated lymphoid tissue (MALT) lymphoma, also referred to as extranodal marginal zone lymphoma [2]. Here, we describe the first case of primary bladder MALT lymphoma that occurred in the setting of interstitial cystitis.

A 68-year-old Japanese female visited our institution with a 2-year history of persistent interstitial cystitis accompanying suprapubic pain and frequent urination. On admission, repeated urine culture showed no evidence of urinary tract infection. Urine cytology resulted in normal study. Treatment of interstitial cystitis was exerted by cystoscopy with hydrodistention, which discovered ulcers and increased vascularity on the bladder wall. Histopathology of the ulcerative lesions was notable for mucosal lymphoid follicles with interstitial infiltration of plasma cells and small lymphocytes (Fig. 1a). Immunophenotype of the lymphoid cells was CD3−, CD5−, CD10−, CD20+, and CD79a+. Deviated expression of immunoglobulin light chain was noted (Fig. 1b). Polymerase chain reaction amplification demonstrated monoclonal rearrangement of *immunoglobulin heavy chain* gene. Computed tomography scan showed a suprapubic mass occupying a portion of the bladder (Fig. 1c). Reduced size and thickened wall of the bladder were consistent with interstitial cystitis. F-18 fluorodeoxyglucose positron emission tomography and bone marrow biopsy were unremarkable. Taken together, we made a diagnosis of stage IE MALT lymphoma of the urinary bladder. Complete remission was recorded after four cycles of rituximab at a standard dose of 375 mg/m^2.

Primary bladder MALT lymphoma is featured by female preponderance and frequent history of chronic infectious cystitis [3]. It rarely disseminates to other organs or tissues and carries an excellent outcome. One explanation for its pathogenesis is that chronic bladder inflammation due to repetitive infection results in accumulation of extranodal lymphoid tissue, as is the case with *Helicobacter pylori* in gastric MALT lymphoma. Indeed, regression of bladder MALT lymphoma is achieved by antibiotic therapy [4]. In contrast, our case seems to have a different etiology because chronic urinary tract infection was absent.

Interstitial cystitis is a chronic inflammatory disorder. Its typical symptoms are suprapubic pain, urinary frequency, urgency, and nocturia. Although heterogeneous, interstitial cystitis possesses some aspects of autoimmunity [5]. The disease primarily affects females, and occasionally occurs in patients with systemic autoimmune diseases. Moreover, possible roles of autoantibodies against muscarinic receptor on the detrusor of the bladder have been suggested.

It is widely known that MALT lymphoma is associated with autoimmune disorders. In this setting, deregulated immune

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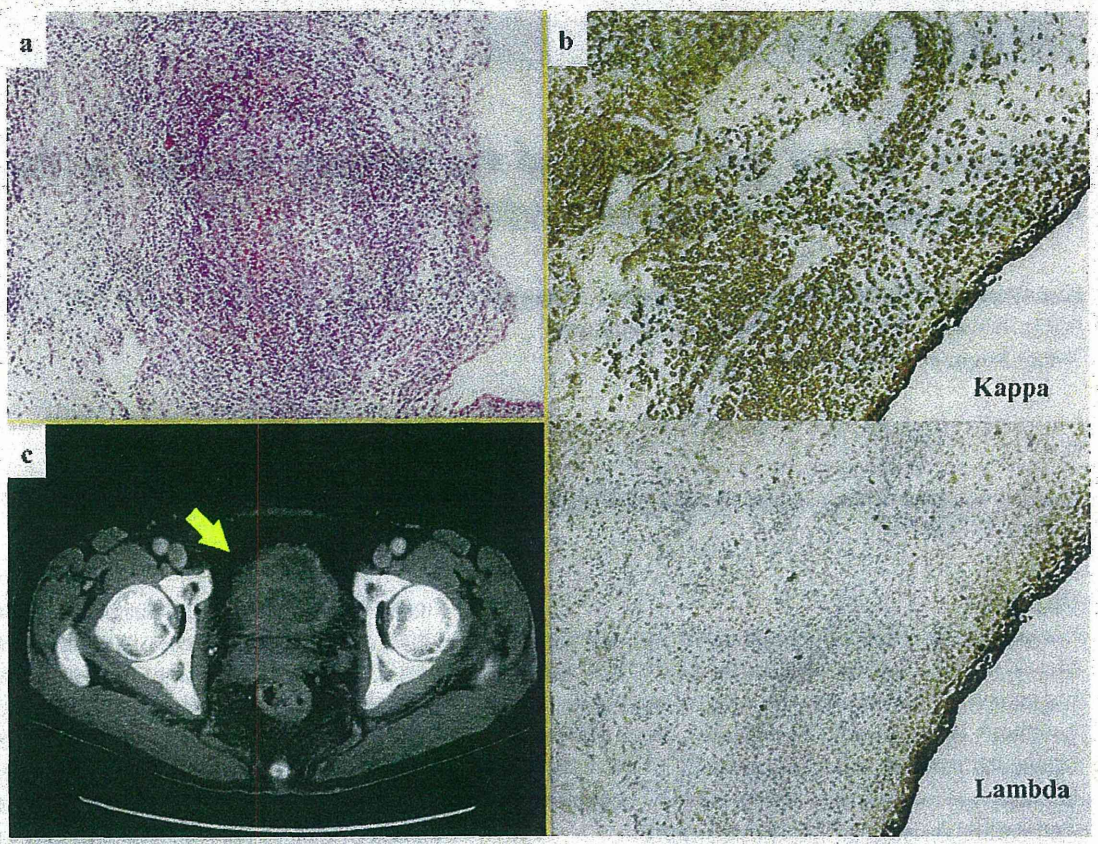

Fig. 1 Primary MALT lymphoma of the urinary bladder. **a** Light microscopic examination detected numbers of lymph follicles in the mucosal epithelium with interstitial infiltration of plasmacytes and small lymphocytes. **b** The lymphoid cells showed deviated expression of immunoglobulin kappa light chain. **c** Computed tomography scan revealed bladder lymphoma (*arrow*), thickened bladder wall, and reduced size of the bladder

response causes chronic inflammation in the target organ, which in turn triggers lymphomagenesis. For example, Sjögren's syndrome and Hashimoto's thyroiditis frequently underlie salivary gland and thyroid MALT lymphoma, respectively [6, 7]. Likewise, interstitial cystitis may result in MALT lymphoma of the urinary bladder.

Finally, presenting symptoms of bladder lymphoma substantially overlap those of interstitial cystitis. In our case, transurethral biopsy of bladder ulcers incidentally led to a diagnosis of MALT lymphoma. Careful follow-up with cystoscopy may help find this rare complication of interstitial cystitis.

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Neurourology and Urodynamics 31:148–155 (2012)

Effects of TRPV4 Cation Channel Activation on the Primary Bladder Afferent Activities of the Rat

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Aims: Transient receptor potential vanilloid 4 (TRPV4) may affect afferent pathways innervating the bladder. We investigated the effects of GSK1016790A (GSK) and RN1734, a TRPV4 agonist and antagonist, respectively, and P2X-purinoceptor antagonists (TNP-ATP and PPADS) on cystometry (CMG), and the effect of GSK on single afferent fiber activities (SAAs) of the rat bladder and its relationship with capsaicin (Cap)-sensitivity. **Methods:** Conscious female Sprague–Dawley rats were used for CMG measurements. In SAA measurements, under urethane anesthesia, SAA was identified by electrical stimulation of the pelvic nerve and by bladder distention. Cystometric parameters were measured before and after intravesical drug instillation. In SAA measurements, response with saline instillation served as baseline. Then, GSK was instilled three times, and finally Cap was instilled to investigate the relationship with Cap-sensitivity. **Results:** Intravesical GSK-instillation transiently decreased bladder capacity and voided volume, which were counteracted by RN1734, TNP-ATP, and PPADS. In SAA measurements, Aδ-fibers (n = 7) were not affected by either GSK or Cap. Based on the Cap-sensitivity, C-fibers could be divided into two subtypes: Cap-insensitive (n = 14) and Cap-sensitive (n = 8). In the Cap-insensitive C-fibers, GSK significantly increased the SAAs during the first instillation, but the increase attenuated with time, whereas GSK did not significantly affect the Cap-sensitive C-fibers. **Conclusions:** The present results suggest that activation of TRPV4 in the bladder, probably urothelium, facilitates the micturition reflex by activation of the mechanosensitive, Cap-insensitive C-fibers of the primary bladder afferents in rats. *Neurourol. Urodynam. 31:148–155, 2012.* © 2011 Wiley Periodicals, Inc.

Key words: afferent nerves; desensitization; rats; transient receptor potential (TRP); urinary bladder

INTRODUCTION

The transient receptor potential vanilloid subfamily (TRPV) contains six proteins in mammals, and they are commonly divided into two subgroups based on sequence homology, functional similarities, and Ca^{2+}-selectivity; TRPV1–V4 and V5/6.[1] The subgroup of TRPV1–V4 members are weakly Ca^{2+}-selective cation channels, modulated by various intracellular signals and activated by temperature.[2,3] Expression of the TRPV1, V2, and V4 has been reported in human and rat/mouse urinary bladders.[4–10] Moreover, TRPV1 has been exploited clinically to desensitize bladder afferents and reduce bladder overactivity.[11] On the other hand, TRPV4 is sensitive to osmotic and mechanical stimuli, such as cell stretching or fluid flow.[12] Some previous studies show that TRPV4 may be modulated by calmodulin (CaM) and adenosine triphosphate (ATP), C-terminal CaM binding potentiating the current and Ca^{2+}-dependent CaM binding to the N-terminal desensitizing the current.[13–16]

Several researchers reported that TRPV4 is implicated in the regulation of urothelial ATP release that modulates the sensitivity of bladder afferent nerves.[7,8,17–19] In our previous study, the activation of the bladder mechanosensitive afferents induced by exogenous ATP was mainly through capsaicin (Cap)-insensitive (probably TRPV1-independent) C-fibers in the rat.[20] Therefore, it is conceivable that TRPV1 and TRPV4 have a role in the bladder afferent transduction via a different pathway.

In the present study, we focused on the afferent function of TRPV4, and investigated the effects of intravesical administration of GSK1016790A (GSK), a TRPV4 agonist, which has at least 300-fold greater potency for activating TRPV4 than 4α-PDD,[21] on single fiber activities of the primary bladder mechanosensitive afferent nerves.

MATERIALS AND METHODS

Animals

Forty-eight adult female Sprague–Dawley rats weighing 180–234 g were used. The rats were maintained under standard laboratory conditions with a 12:12 h light:dark cycle, and free access to food pellets and tap water. The protocol was approved by Animal Ethics Committees of The University of Tokyo Graduate School of Medicine and in line with NIH guidelines for the care and use of experimental animals.

Cystometry (CMG) Measurements

Rats were anesthetized with 30 mg/kg intraperitoneal pentobarbital sodium. A polyethylene catheter (Clay-Adams PE-50; Parsippany, NJ) was inserted in the bladder through the dome, and secured. After the operation, each rat was housed single in a cage.

Lori Birder led the review process.
Conflict of interest: none.
Grant sponsor: Ministry of Education, Culture, Sport, Science and Technology of the Japanese Government; Grant numbers: 40159588, 80595257.
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Received 13 June 2011; Accepted 29 July 2011
Published online 28 October 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.21212

Continuous CMG was performed on conscious rats 4 days after surgery. Each rat was placed without any restraint in a metabolic cage (3701M081; Tecniplast, Buguggiate, Italy) for at least 1 hr to adapt to the environment. The bladder catheter was connected to a pressure transducer (DX-100; Nihon Kohden, Tokyo, Japan) and microinjection syringe pump (KDS100; Muromachi, Tokyo, Japan) via a three-way tap. Saline at room temperature was continuously infused into the bladder at a rate of 0.08 ml/min. The basal pressure (BP; cmH_2O), micturition threshold (MT; cmH_2O), peak pressure (PP; cmH_2O), and voided volume (VV; ml) were recorded continuously on data acquisition program (Windaq; DATAQ Instruments Inc., Akron, OH). Bladder capacity (BC; ml) was calculated as intercontraction interval (ICI) × saline infusion rate into the bladder. All parameters were averaged for 20 min (10–30 and 40–60 min after drug administration), and investigated before and after drug instillation.

Afferent Measurements

The rats were anesthetized with urethane (1.5 g/kg intraperitoneally). Body temperature was maintained by a heated blanket at 38°C. Single afferent fiber measurements were performed as described before.[20,22,23] In brief, the left pelvic nerve was dissected from surrounding tissue proximal to the major pelvic ganglion. A pair of silver electrodes was placed around the pelvic nerve. A polyethylene catheter (Clay-Adams PE-50) was inserted in the bladder. Both L6 dorsal roots were cut close to their entrance to the spinal cord after the laminectomy. Fine filaments were dissected from the left L6 dorsal root and placed across shielded bipolar silver electrodes. Clearly different unitary action potentials of afferent fiber originating from the bladder were identified by electrical stimulation of the pelvic nerve and bladder distention with saline. These action potentials were discriminated by the Spike2 (CED, Cambridge, UK) impulse shape recognition program. Conduction velocity (CV) was calculated from the latency of response to electrical stimulation and the conduction distance between stimulation and recording sites, which was based on our anatomical data. Fibers were grouped based on CV. Those with a CV < 2.5 m/sec were considered to correspond to unmyelinated C-fibers and those with CV ≥ 2.5 m/sec to thinly myelinated Aδ-fibers.[24]

Protamine sulfate (PS) solution (10 mg/ml, 0.3 ml) was instilled intravesically and kept in the bladder for 60 min just before the measurement. Single fiber afferent activity was recorded during constant filling CMG with saline at 0.08 ml/min. Filling continued until an intravesical pressure of 30 cmH_2O was reached. The afferent activity caused by pelvic nerve stimulation was also recorded before and after bladder filling and confirmed to correspond with that caused by bladder filling.

At the beginning of the experiments, recording was repeated consecutively three times, at 5 min intervals to evaluate the reproducibility. The third recording served as the baseline value. After that, GSK was instilled three times according to the same time schedule as before GSK instillation; all three cycles of recording were used to evaluate the time-dependency and reproducibility of the drug effect. Then finally, Cap was instilled to investigate the relationship with Cap-sensitivity. The bladder was not washed out between each of multiple instillations.

Unitary afferent activity was evaluated in relation to intravesical pressure and volume. The relationship of nerve activity to pressure or volume was established by comparing nerve activity and intravesical pressure at 1-sec intervals. These values were then averaged at 5 cmH_2O interval of pressure or by dividing into five equal parts of volume in the filling phase. Average unitary activity was totaled as a function of intravesical pressure or volume. Afferent nerve activity is expressed as a percentage of baseline activity, integrated for the whole filling phase. Since the stimulation substance instillation into the bladder increased the afferent activity approximately 150% as significant changes in our previous studies,[20,22,23] "Cap-sensitive" or "Cap-insensitive" afferent activities were classified based on both pressure and volume increases of more or less than 150% from baseline, respectively, when the bladder was instilled with Cap.

Drugs

Protamine sulfate, GSK1016790A (*N*-((1*S*)-1-{[4-((2*S*)-2-{[(2,4-dichlorophenyl) sulfonyl]amino}-3-hydroxypropanoyl)-1-piperazinyl]carbonyl}-3-methylbutyl)-1-benzothiophene-2-carboxamide),[21,25] and Cap were purchased from Sigma–Aldrich (St. Louis, MO). RN1734 (2,4-dichloro-*N*-isopropyl-*N*-(2-isopropylaminoethyl) benzenesulfonamide)[26] and PPADS (pyridoxal phosphate-6-azo (benzene-2,4-disulfonic acid)) were purchased from Tocris Bioscience (St. Louis, MO). TNP-ATP (2′,3′-*O*-(2,4,6-trinitrophenyl-)ATP) solution was purchased from Molecular Probes (San Diego, CA). GSK and RN1734 were dissolved in *N,N*-dimethylacetamide (DMA), and Cap was dissolved in absolute ethanol as a stock solution. These drugs were stored at −80°C and subsequent dilutions of the drugs were made on the day of the experiment using saline. TNP-ATP and PPADS were diluted/dissolved in saline. PS was dissolved in distillated water. All drugs were instilled intravesically. The doses were chosen according to previous studies in the mouse/rat and our pilot study.[7,20,21,26]

Statistical Analysis

All data are expressed as mean ± SEM. Results were analyzed using two-way ANOVA followed by Tukey's test for multiple comparisons before and after drug instillation. P values <0.05 are considered statistically significant.

RESULTS

CMG Measurements

Instillation of the vehicle (0.4% DMA) did not affect cystometric parameters (data not shown). Instillation of GSK significantly reduced BC and VV at 10–30 min; however, the effects were attenuated 40–60 min after instillation (Table I and Fig. 1A).

Instillation of RN1734, TNP-ATP, and PPADS induced no significant changes in cystometric parameters, although BC and VV tended to be increase and PP tended to decrease. When instilled in combination with RN1734, TNP-ATP, or PPADS GSK did not affect any of the cystometric parameters (Table I and Figs. 1A and 2).

Afferent Measurements

In a pilot study, we have investigated whether the both Aδ- and C-fiber afferent activities were influenced by 1 hr PS-exposure but no significant differences were found between before and after PS-exposure (Aδ-fibers; n = 7, base: 100%, after PS-exposure: 95% and 102% based on pressure and volume, respectively. C-fibers; n = 6, base: 100%, after PS-exposure: 102% and 98% based on pressure and volume, respectively).

TABLE I. The Effects of Intravesical Application of GSK1016790A (GSK), RN1734, TNP-ATP, and PPADS on Cystometric Parameters

Parameter	Saline	10–30 min after instillation of GSK	40–60 min after instillation of GSK
GSK1016790A (3×10^{-6} M, TRPV4 agonist), n = 6			
Base pressure (cmH_2O)	3.13 ± 0.56	2.61 ± 0.89	2.71 ± 0.54
Micturition threshold (cmH_2O)	9.61 ± 1.26	7.43 ± 0.50	8.15 ± 1.05
Peak pressure (cmH_2O)	43.54 ± 5.54	42.23 ± 3.44	45.05 ± 5.64
Bladder capacity (ml)	1.42 ± 0.23	0.75 ± 0.25*	1.14 ± 0.11
Voided volume (ml)	1.44 ± 0.22	0.84 ± 0.26*	1.20 ± 0.13

Parameter	Saline	10–30 min after instillation of RN1734	40–60 min after instillation of RN1734	10–30 min after instillation of GSK and RN1734	40–60 min after instillation of GSK and RN1734
GSK1016790A (3×10^{-6} M, TRPV4 agonist) and RN1734 (10^{-5} M, TRPV4 antagonist), n = 6					
Base pressure (cmH_2O)	3.38 ± 0.44	3.09 ± 0.42	3.18 ± 0.54	2.8 ± 0.41	3.68 ± 0.57
Micturition threshold (cmH_2O)	8.21 ± 0.73	8.86 ± 1.98	9.77 ± 2.12	8.85 ± 0.75	10.17 ± 1.41
Peak pressure (cmH_2O)	47.69 ± 3.10	42.45 ± 2.99	46.06 ± 3.28	42.02 ± 2.28	49.83 ± 3.37
Bladder capacity (ml)	1.32 ± 0.22	1.30 ± 0.19	1.69 ± 0.27	1.63 ± 0.07	1.39 ± 0.29
Voided volume (ml)	1.33 ± 0.23	1.36 ± 0.19	1.63 ± 0.27	1.60 ± 0.08	1.44 ± 0.30

Parameter	Saline	10–30 min after instillation of TNP-ATP	40–60 min after instillation of TNP-ATP	10–30 min after instillation of GSK and TNP-ATP	40–60 min after instillation of GSK and TNP-ATP
GSK1016790A (3×10^{-6} M, TRPV4 agonist) and TNP-ATP (3×10^{-5} M, $P2X_3$ antagonist), n = 6					
Base pressure (cmH_2O)	1.97 ± 0.56	2.68 ± 0.32	2.79 ± 0.54	2.28 ± 0.25	2.26 ± 0.44
Micturition threshold (cmH_2O)	12.27 ± 1.89	9.66 ± 1.00	11.95 ± 1.32	9.04 ± 1.55	7.29 ± 0.91
Peak pressure (cmH_2O)	41.42 ± 3.48	36.77 ± 2.61	35.43 ± 3.64	37.73 ± 3.68	38.74 ± 5.26
Bladder capacity (ml)	1.31 ± 0.18	1.00 ± 0.17	1.44 ± 0.13	1.33 ± 0.13	1.16 ± 0.24
Voided volume (ml)	1.43 ± 0.17	1.13 ± 0.15	1.59 ± 0.09	1.44 ± 0.17	1.16 ± 0.23

Parameter	Saline	10–30 min after instillation of PPADS	40–60 min after instillation of PPADS	10–30 min after instillation of GSK and PPADS	40–60 min after instillation of GSK and PPADS
GSK1016790A (3×10^{-6} M, TRPV4 agonist) and PPADS (3×10^{-5} M, nonselective P2X antagonist), n = 6					
Base pressure (cmH_2O)	2.99 ± 0.53	2.43 ± 0.62	3.09 ± 0.81	2.58 ± 0.69	2.70 ± 0.46
Micturition threshold (cmH_2O)	9.17 ± 1.89	9.48 ± 2.02	10.09 ± 2.16	7.83 ± 2.23	9.39 ± 1.12
Peak pressure (cmH_2O)	50.63 ± 5.30	39.77 ± 3.76	40.80 ± 3.67	46.01 ± 6.56	48.28 ± 2.49
Bladder capacity (ml)	1.20 ± 0.23	0.99 ± 0.28	1.48 ± 0.22	1.07 ± 0.27	1.14 ± 0.18
Voided volume (ml)	1.26 ± 0.25	1.07 ± 0.31	1.55 ± 0.22	1.13 ± 0.29	1.19 ± 0.18

Values are indicated as mean ± SEM.
*$P < 0.05$: significant difference from base (two-way ANOVA followed by Tukey's test).

A total of 29 single-unit afferent fibers were isolated in 24 rats (maximum 2 fibers per 1 rat); 7 units corresponded to criteria for myelinated Aδ-fibers (CV: 3.80 ± 0.66 m/sec), and 22 for unmyelinated C-fibers (CV: 1.80 ± 0.09 m/sec). After GSK instillation, bladder compliance did not change significantly (baseline: 0.0223 ± 0.0011 ml/cmH_2O, GSK-1st instillation: 0.0247 ± 0.0011 ml/cmH_2O, GSK-2nd instillation: 0.0217 ± 0.0012 ml/cmH_2O, GSK-3rd instillation: 0.0220 ± 0.0015 ml/cmH_2O). The afferent activity of the Aδ-fibers did not change after either GSK or Cap instillation (Figs. 3A and 4). The afferent activities of C-fibers were divided into two groups by the Cap-sensitivity; Cap-insensitive (Fig. 3B) and Cap-sensitive (Fig. 3C). Among 22 discriminated C-fiber single units, 14 units were classified as the Cap-insensitive fibers, and the remaining 8 units as the Cap-sensitive fibers. Upon GSK instillation activities of the Cap-insensitive fibers in response to the bladder filling increased significantly at the first instillation, but the effect of GSK gradually attenuated at the second and third instillations (Fig. 4). The activities of Cap-sensitive C-fibers showed no significant change by GSK instillation (Fig. 4).