REVIEW OF THE INTERNATIONAL CONTINENCE SOCIETY 45th ANNUAL SCIENTIFIC MEETING 6-9 October 2015, Montreal, Canada

Jane Meijlink

In recent years, the International Continence Society (ICS) has increasingly developed a special interest in pelvic dysfunction and pelvic pain, including interstitial cystitis/bladder pain syndrome (IC/BPS) and hypersensitive bladder (HSB) in addition to the field of incontinence. This has made the ICS annual scientific meeting an important date in the conference calendar for those with a focus on IC/BPS. This year's meeting in Montreal was no exception with podium sessions on research, a selection of workshops in the field of pelvic pain and dysfunction, bladder sensation, pudendal neuralgia, a round table discussion on urgency (which rather regrettably focused on overactive bladder urgency only, with painful urgency as in IC/BPS largely forgotten), an update on IC/BPS, vestibulodynia and pelvic pain syndromes in the Pan-Arab Continence Society (PACS) session (stressing multimodal treatment and a multidisciplinary team), while a large part of the final morning was devoted to understanding pelvic pain and – a first for the ICS – a round table discussion and presentations around the topic of bladder pain syndrome/interstitial cystitis: pain and phenotypes.

Round Table: Understanding Pelvic Pain

Neuroplasticity and Pain Chronification was the topic presented by Fernando Cervero, Professor of Anaesthesia in Montreal, looking at the role of the urothelium in the signalling of sensory events in the bladder. He explained that central sensitization is a generator of pain hypersensitivity by central neural plasticity. Central sensitization is responsible for many of the temporal, spatial and threshold changes in pain sensibility in acute and chronic clinical pain settings and exemplifies the fundamental contribution of the central nervous system to the generation of pain hypersensitivity. Central sensitization is a condition of the nervous system that is associated with the development and maintenance of chronic pain. When central sensitization occurs, the nervous system goes through a process called 'wind-up' and gets regulated in a persistent state of high reactivity. This persistent, or regulated, state of reactivity subsequently comes to maintain pain even after the initial injury might be healed.

Professor Jeffrey Mogil from the Department of Psychology in Montreal looked at **Sex differences in pain in mice and humans**, noting that 70% of chronic pain patients are women. This may have implications for analgesic development.

Professor Yukio Homma, urologist from Tokyo explained the East Asian concept of **Hypersensitive bladder (HSB) – its clinical and biological implications.**
HSB is a condition with

1) Hypersensitive bladder symptoms (pain, pressure or discomfort in the bladder, usually with urinary frequency and nocturia)
2) No confusable diseases (infection, malignancy, stone, endometriosis etc.)

He briefly looked at the different terms used for IC or IC-like conditions:

- Interstitial cystitis (IC)
- Painful bladder syndrome (PBS)
- Bladder pain syndrome (BPS)
- IC/PBS, IC/BPS, PBS/IC, BPS/IC
- Chronic pelvic pain syndrome (CPPS)

He asked: are they used with distinct meanings? IC/PBS, IC/BPS, PBS/IC, BPS/IC are used interchangeably and lead to confusion in clinical practice and research. Usage of the different terms is ambiguous. PBS/IC (etc.) can be a symptom complex, a syndrome or a disease.

Professor Homma questioned use of the word **Pain** or **Painful** in terms for IC or IC-like conditions, querying whether Pain in fact fully describes IC symptoms.
Referring to the International Association for the Study of Pain (IASP) definition of pain: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", he noted that in this context pain in its broader sense may include pressure or discomfort. Pain is, he feels, too restrictive to describe symptoms experienced by IC patients. Unpleasant sensations are suggestive of visceral hypersensitivity.
Professor Homma suggests that the advantages of HSB are that it represents symptoms more broadly than just pain and suggests an upregulated nociceptive sensation pathway, which causes unpleasant sensations. The East Asian definitions are as follows:

- IC = HSB symptoms and cystoscopic abnormality
- HSB = HSB symptoms alone

According to Professor Homma, these definitions are sensible and understandable from clinical and biological perspectives.

Round Table Discussion: Bladder Pain Syndrome/Interstitial Cystitis: Pain and Phenotypes

Session co-chairs Professor James Gillespie (physiologist) and Dr Jos Houbiers (Astellas Pharma) introduced the ICS objectives and theme. Sensation was the theme of ICS 2015 and this was the first time that such a round table had been held on IC/BPS at ICS. Dr Houbiers noted that the pain and urgency of IC/BPS fit nicely into the ICS 2015 theme of sensation.
Professor Gillespie started the session with **Notes on the micro-anatomy of the bladder**, stressing that we still know relatively little of the distribution and types of nerves in the bladder or urethra involved in sensation and pain.

IC/BPS and chronic pelvic pain expert Professor Robert Moldwin followed with a presentation on **BPS/IC symptoms and phenotypes: the only way forward in this heterogeneous disease.**
He presented a 'plan of attack' based on possible phenotypes:

<u>End Organ Inflammatory event</u>

- Treat local pathology
- Nerve blocks
- Neurostimulation
- Centrally acting agents

<u>Peripheral Nerve Dysfunction</u>

- Nerve blocks
- Neurostimulation
- Centrally acting agents

<u>Central Nerve Dysfunction</u>

- Centrally acting agents

If the patient is not getting better and therapy appears to be ineffective, he suggested that another diagnosis or co-existing conditions should be considered.
Ask yourself, he said, if it is possible that this patient has multiple pain generators?

- Alternating constipation and diarrhea?
- Painful sexual intercourse?
- Generalized muscle and joint pain?

He underlined that a detailed history and physical examination are crucially important and will produce valuable information.

Ingredients of pelvic pain may include: constipation, pelvic floor dysfunction, fibromyalgia, IC/BPS, vulvodynia, CP/CPPS. The question is then: which is the MAJOR PLAYER?

He took a look at provoked vulvodynia and pelvic floor dysfunction (myalgia) in the IC/BPS patient and suggested that you could consider giving the patient treatment for pelvic floor dysfunction such as:

- Behavioural changes, biofeedback, physical therapy
- Bowel regime
- Topical heat
- Skeletal muscle relaxants

If the response is favourable, continue the therapy. If there is no response, evaluate for IC/BPS.

He looked at the use of intravesical anaesthetics for the diagnosis of bladder-based pain. The anaesthetic should be instilled with cystoscopy and held 15-30 minutes. If the pain disappears, the bladder is the likely source of pain. If the pain continues, the source of pain is unclear. The value of the cystoscopic anaesthetic challenge is the diagnostic potential, enhancement of physical examination and therapeutic potential.

Like others at this ICS meeting, Professor Moldwin emphasized the need for a multidisciplinary team approach, with the urologist/urogynaecologist involving:

→ Pain clinics
→ Rheumatologists
→ Nutritionists
→ Expert physical therapists
→ Psychologists, sex therapists
→ Acupuncturists
→ Primary care physicians
→ Other staff

SUMMARY:

- Phenotyping patients will result in better clinical outcomes
- A complete history and physical examination is ESSENTIAL
- Algorithm of management based on the MAJOR PLAYER
- Further management based on quality of life

Dr Melissa Farmer (psychology and physiology) spoke on: **The (mal)adapting brain: parsing the dynamic mechanisms or urologic pelvic pain, exploring the mechanisms that may underlie unusual symptom patterns, promoting mechanism-based assessment of bladder pain and establishing the critical role the brain plays in chronic bladder pain.**
She emphasized that different mechanisms underlie pain onset and maintenance. You cannot infer initiating factors from the chronic phenotype. Emotional learning drives neuroplasticity underlying reorganization of brain function and structure and that multi-dimensional pain may require compound treatments to address each dimension.

Dr Olivier van Till (Astellas Pharma) described a drug trial that didn't work out, but unexpectedly led to a particularly interesting exploratory study: **Symptoms in BPS/IC comparing patients with to those without Hunner lesions (HL) and looking at whether patients with and without HL are different in the clinical presentation.**
Looking at Hunner lesion, he noted that HL is the only consistent cystoscopic finding that leads to a diagnosis of BPS/IC. It should not to be confused with glomerulations (i.e. pinpoint petechial hemorrhages in the bladder wall), which are not specific for BPS/IC. Experienced urologists can detect a majority of Hunner lesions at plain cystoscopy, but for optimal treatment results all Hunner lesions have to be identified and treated and that requires hydrodistension. Treatment of HL appears to constitute one of the few BPS/IC therapies that result in improvement measured in months with only a single exposure to the procedure. (AUA Guideline 2014). Dr van

Till found that patients with lesions (HL+) tended to be older and have more bladder-related comorbidities. Using UPOINT, HL+ seemed to be a more bladder-related phenotype. The currently controversial glomerulations are not specific for Hunner lesion. Baseline disease severity, pain and quality of life appeared to be worse for Hunner lesion. Dr van Till noted that the limitation to this study was that only moderate to severe patients were included.
He suggests that HL+ medical history and phenotyping point towards more involvement of bladder. Non lesion appears to be less organ-specific.
Hypothesis:

- HL+ is a bladder-centred condition
- HL- is a centralized chronic pain condition

From this preliminary exploratory study, it looked as though voiding frequency and pain seemed to be related in patients with Hunner lesion, but unrelated in non-lesion patients.

Professor J. Quentin Clemens, Michigan, MAPP Network Chair, provided an overview of **Clinical phenotyping of IC/BPS in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network**, with a focus on clinical phenotyping.
Urologic Chronic Pelvic Pain Syndrome (UCPPS) is a general term used in the MAPP Network studies to describe idiopathic chronic pelvic pain of urologic origin. Within this context, this term includes interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. In the MAPP Epidemiology-Phenotyping Study, they found that psychosocial symptoms were similar in UCPPS subjects and "positive" controls with fibromyalgia, IBS and chronic fatigue syndrome. These chronic overlapping pain conditions were discovered in 43% female UCPPS patients and 30% male. This group of patients had more severe UCPPS symptoms, worse quality of life and more psychosocial symptoms.
In relation to the Bladder-Sensitivity Phenotype, they have been looking at questions from the RAND Interstitial Cystitis Epidemiology Study (RICE) case definition concerning urinary urgency due to pain/pressure/discomfort and pain that worsens with bladder filling. Responses suggest an overlap in symptoms between IC/BPS and CP/CPPS.
Bladder hypersensitivity appears to be associated with more severe UCPPS symptoms, more non-urologic pain and worse quality of life.
In relation to symptom assessment, baseline questionnaire responses were examined using principle components and exploratory factor analysis. Two factors provided the best psychometric description of items: pain symptoms and urinary symptoms. There were equivalent results in men and women.
He concluded by saying that clinical phenotyping of UCPPS patients should focus on at least 3 important factors:

- Pain localization (presence of pain outside the pelvis);
- Presence of chronic overlapping pain conditions;
- Bladder hypersensitivity.

He also suggested that we should consider abandoning 'total symptom scores' and instead utilize dual outcomes (pain symptoms, urinary symptoms).

Symptoms Flares seem to be more common with the 'centralized' phenotype and with more severe bladder symptoms ('bladder' phenotype). Flares vary in symptom type, severity and duration (minutes to days), are unpredictable and lead to social avoidance and isolation.
On MAPP Neuroimaging Studies, he reported structural and functional brain changes consistent with previously reported findings in other chronic pain conditions. These include changes in brain sensorimotor regions affecting sensory processing and motor control in the pelvic floor region; furthermore, the primary somatosensory cortex, pre-supplemental motor area, hippocampus, amygdala, posterior insula and cerebellum. He noted that the patterns distinguish UCPPS patients from controls and also correlate with UCPPS symptom severity.
Future directions of the MAPP Study: the second phase of the MAPP Research Network is expected to run from 2015 to 2019. The studies will include:

- Assessment of symptom patterns and corresponding biologic change through longer follow-up
- Evaluation of promising candidate biomarkers

- Longitudinal neuroimaging and quantitative pain testing
- In-depth assessment of treatment response
- Identification of clinically relevant UCPPS patient sub-groups.

The MAPP Network home page contains much useful information about the MAPP studies: http://www.mappnetwork.org/

A SELECTION OF ABSTRACTS IN THE FIELD OF PELVIC PAIN, IC/BPS, HYPERSENSITIVE BLADDER AND KETAMINE CYSTITIS PRESENTED AT ICS 2015.

Abstract 19

BEHIND THE ULCER TYPE IC – AN ANALYSIS OF THE CORRELATION AMONG CLINICAL SYMPTOMS, IMMUNOCHEMICAL STUDY, COMPUTERIZED TOMOGRAPHY, AND HISTOPATHOLOGY FINDINGS BETWEEN ULCER AND NON-ULCER TYPE IC/BPS

Jhang J, Jiang Y, Kuo H

This immunohistochemical study from Taiwan concerned differences/similarities between ulcer (lesion) and non-ulcer (non-lesion) IC/BPS. The authors noted that current consensus suggests that patients with IC/BPS can be subdivided into two types: ulcerative and non-ulcerative. The clinical characteristics in the patients with ulcerative and non-ulcerative IC/BPS are different, but the pathophysiology and underlying mechanism differences between these patients were still unclear. The objective of this study was to investigate the urothelium dysfunction in patients with ulcerative and non-ulcerative IC/BPS. The authors found that patients with ulcer IC/BPS had more severe clinical symptoms in VAS pain scale, specific focal bladder wall thickening in CT image, bladder eosinophil infiltration and denudation in histopathology examination, higher cell apoptosis, urothelial dysfunction and inflammation in immunochemical staining than non-ulcer IC/BPS. Furthermore, the histopathology finding of urothelium denudation could be correlated to clinical symptoms and immunochemical staining. They concluded that ulcer and non-ulcer IC/BPS are similar clinical syndromes with different symptom severity, image, histopathology and immunochemical findings. Ulcer and non-ulcer IC/BPs might be considered as two different diseases, or one disease with different severity, and the pathogenesis difference should be investigated.

Abstract 20

HUNNER TYPE INTERSTITIAL CYSTITIS IS A DISTINCT INFLAMMATORY DISORDER CHARACTERIZED BY EPITHELIAL DENUDATION AND FREQUENT PRESENCE OF LIGHT CHAIN-RESTRICTED B-CELLS, IMPLYING INVOLVEMENT OF IMMUNE RESPONSES IN THE PATHOGENESIS

Akiyama Y, Maeda D, Morikawa T, Niimi A, Nomiya A, Sugiyama R, Kamei J, Ichihara K, Aizawa N, Igawa Y, Fukayama M, Homma Y.

Pathological investigation of interstitial cystitis (IC) has not been performed in detail, partly due to the purported lack of characteristic pathological findings and the trend for it to be diagnosed only by clinical findings. In the past, inflammatory cell infiltration, predominantly composed of lymphocytes, plasma cells and denudation of epithelium had been documented as major pathological findings of IC. To investigate pathological features of IC in more detail, Akiyama and colleagues from Tokyo scrutinized these pathological findings in a more objective and accurate manner by applying novel image-analysing software, especially regarding the presence of light chain restricted plasma cells to explore clonal B-cell expansion. Diagnosis of IC was made according to Asian clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Patients with IC were classified into either Hunner type IC (HIC) or Non-Hunner type IC (NHIC) by the presence/absence of the Hunner lesions on cystoscopy. The results of this study suggest that HIC is an inflammatory disorder characterized by epithelial denudation and pancystitis, which should be distinctly distinguished from NHIC. The presence of light chain-restricted plasma cells implies clonal expansion of B-cells, which is frequently observed in a variety of inflammatory diseases, especially in association with autoimmunity or chronic infection. A B-cell population abnormality may be involved in the pathogenesis of HIC. The authors concluded that HIC is a distinct inflammatory disorder characterized by epithelial denudation and frequent presence of expansion of light chain-restricted B-cells, suggesting involvement of immune responses in its pathogenesis.

Abstract 21

USERS EXPERIENCES OF KETAMINE BLADDER SYNDROME (KBS)

Logan K, Gill P, Shaw C, John B, Madden K

Ketamine is a dissociative drug used in anaesthesia, palliative pain care and veterinary medicine. It is also used recreationally as a 'club drug', mainly snorted in powder form. While the precise aetiology is unclear, when used regularly and in increasingly higher doses, ketamine can cause considerable and potentially irreversible damage to the bladder and urinary tract, resulting in ulceration, fibrosis, bleeding, pain, urgency, frequency and incontinence. The prevalence of KBS is unclear but believed to be increasing. Little is yet known about how patients are affected by KBS, their understanding of the condition, their rationale for seeking medical help or their experiences of healthcare services. This study from Cardiff aimed to explore ketamine users' experiences of KBS, along with associated healthcare provision issues. Four key themes emerged from their analysis:

- Ketamine use and associated bladder symptoms
- Pain experience and pain management
- The psychosocial impact of KBS
- Healthcare services experiences.

The results demonstrated a need for a more compassionate and preventative approach to addressing the issues faced by these vulnerable young people. There is a need for more awareness of KBS among clinicians and GPs. Health promotion and harm reduction strategies are required to raise awareness and advice/support are needed for ketamine cessation. These are challenging patients due to the complexity of the substance misuse. This information will become increasingly important as experimental/recreational drug usage becomes more common place within teenage and young people's culture. The study highlights the need for a more integrated, multi-agency approach, which incorporates an appropriate primary care assessment, timely diagnoses and referral to specialist urological, pain management and substance misuse teams.

Abstract 22

HYDRODISTENTION OF THE BLADDER FOR THE TREATMENT OF PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS (PBS/IC)

The purpose of this study from the USA was to determine whether a transvaginal trigonal nerve block immediately preceding cystoscopy with hydrodistention yields an additional therapeutic benefit compared to cystoscopy with hydrodistention alone for the treatment of painful bladder syndrome/interstitial cystitis (PBS/IC). Hydrodistention was shown to yield a statistically significant improvement in postoperative pain scores. This improvement was irrespective of trigonal nerve block or distention times. However, an opportunity for bias exists as the decision to perform a trigonal block as well as determine the distention time was dependent on the surgeon. According to the authors, trigonal nerve block did not show any improvement in pain scores at 1-month postoperative visit and hydrodistention of the bladder was shown to decrease pain postoperatively regardless of trigonal nerve block or time of distention. Given the surgeon bias in this study, a randomized-controlled trial is necessary to determine the benefits of length of hydrodistention or performance of a block.

Abstract 23

A PHASE 2 STUDY IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS) OF THE NOVEL P2X3 ANTAGONIST AF-219

Moldwin R, Kitt M, Mangel J, Beyer R, Hanno P, Butera P, Ford A.

P2X3 receptors are located selectively on primary afferent neurons. P2X3 purinoceptors drive sensitization of bladder sensory neurons in response to ATP, causing chronic symptoms of pain, discomfort and urgency. Furthermore, P2X3 knock-out mice displayed bladder hyporeflexia and P2X3 inhibition suppresses visceral hyperalgesia in rodent models. Based upon these findings, Moldwin and colleagues' hypothesis was that a P2X3 antagonist, AF-219, would reduce interstitial cystitis/ bladder pain syndrome (IC/BPS) symptoms. This was a randomized, double-blind, placebo controlled study in women with IC/BPS with moderate to severe pain. The objective was to determine the efficacy (pain scores) and safety of treatment with AF-219 or placebo for 4-weeks. Patients treated with AF-219 had improvement in the key symptoms of IC/BPS: pain scores, urinary urgency and general improvement in patient reported symptoms. AF-219 was generally well tolerated after titration was implemented in the study. AF-219 has the potential to be an important treatment option in

patints with IC/BPS. Based on the results of this study there should be further evaluation of AF-219 in patients with IC/BPS.

Abstract 24

CLINICAL COMPARISON OF INTRAVESICAL HYALURONIC ACID AND CHONDROITIN SULPHATE THERAPY FOR BLADDER PAIN SYNDROME/INTERSTITITAL CYSTITIS

Gülpinar Ö, Kayis A, Akinci A, Esen B, Süer E, Gökçe M.

In this study from Turkey, patients with history of bladder pain syndrome/interstitial cystitis(BPS/IC) are compared for clinical efficacy of intravesical hyaluronic acid (HA) or chondroitin sulphate (CS) therapy. With 6 months follow up of patients with BPS/IC, both CS and HA instillations reduced symptoms significantly with no severe adverse effects. Intravesical CS is superior to intravesical HA in terms of 24 hour frequency, nocturia and ICPI in patients with BPS/IC in short term period.

Abstract 26 (MAPP Network)

PAINFUL BLADDER FILLING AND PAINFUL URGENCY ARE DISTINCT CHARACTERISTICS IN MEN AND WOMEN WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROMES (UCPPS) – A MAPP RESEARCH NETWORK STUDY

Lai H, Krieger J, Pontari M, Buchwald D, Hou X, Landis J.

"Painful filling" (i.e. pain that gets worse with bladder filling), and "painful urgency" (the urge to urinate due to pain, pressure, or discomfort instead of fear of leakage) have been described in women with interstitial cystitis (IC/BPS). The clinical significance of painful filling and painful urgency is not well understood in either women or men. The objectives of this study were to 1) describe bladder pain symptoms in women and men with UCPPS, and (2) correlate these to urologic and non-urologic symptoms or syndromes, and psychosocial measures. The MAPP Research Network enrolled 233 female and 191 male UCPPS participants with IC/BPS and/or CP/CPPS. Participants were asked if their pain was worse with bladder filling ("painful filling"), or if their urge to urinate was because of pain, pressure, or discomfort ("painful urgency"). Participants were then categorized into 3 groups: 1) "both" painful filling and painful urgency, 2) "either" painful filling or painful urgency, or 3) "neither". 24.6% of males and 11.6% of females had neither painful filling nor painful urgency. 34.6% of males and 36.9% of females had either painful filling or painful urgency. 40.8% of males and 59.2% of females reported both painful filling and painful urgency. The percentage of UCPPS men who reported bladder pain symptoms was surprisingly high (75.4%). Among men and women, presence of "painful filling" and/or "painful urgency" was associated with more severe urologic symptoms (worse pain, frequency, urgency), higher physical symptom burden, higher depression scores, and worse SF-12 physical health. Men but not women were more likely to have irritable bowel syndrome, catastrophizing, or report a current UCPPS "flare". Females were more likely to have chronic fatigue syndrome, higher fatigue scores, negative affect, and worse SF-12 mental health in the same pattern. A surprising large percentage of men with UCPPS reported symptoms consistent with bladder hypersensitivity. Future research efforts, particularly involving UCPPS males, should use tools such as the RICE questionnaire to assess bladder pain characteristics ("painful filling" or "painful urgency"). Male and female UCPPS participants with "painful filling" and/or "painful urgency" have more severe urologic symptoms, more generalized symptoms, and poorer quality of life than those with neither of these bladder characteristics. UCPPS patients with these bladder characteristics may represent distinct subgroups or phenotypes.

Abstract 27

INTRAPELVIC NERVE ENTRAPMENTS – A NEGLECTED CAUSE OF PERINEAL PAIN AND URINARY SYMPTOMS.

Lemos N, Marques R, Sparapani F, Plöger-Schor C, Schor E, Girão M.

The intrapelvic portions of the lumbosacral nerves are best approached by laparoscopy. However, in addition to lower urinary tract symptoms and unilateral perineal pain, intrapelvic nerve entrapments usually produce symptoms that are not associated with urologic or gynecologic practice, such as sciatica. The aim of this study from Brazil was to evaluate the outcomes of the patients submitted to the laparoscopic decompression of lumbosacral nerves, as well as the delay in diagnosis. Perioperative complications were: one pudendal nerve transection, one obturator nerve tearing due to excessive traction during exposure, one case of bladder hypoesthesia, one ureteral lesion and one case of rectal pain. The authors concluded that intrapelvic nerve entrapment is a neglected cause of perineal pain and LYTS, taking on average 5 years and two unnecessary

surgical procedures before diagnosis. The laparoscopic detrapment of intrapelvic nerves produces satisfactory, reproducible results.

Abstract 188

URODYNAMIC EFFECT OF INTRAVESICAL AND INTRATHECAL ADMINISTRATION OF SELECTIVE E-SERIES PROSTAGLANDIN 4 RECEPTOR ANTAGONIST, ONO-AE3-208, ON CYCLOPHOSPHAMIDE INDUCED CYSTITIS RATS

Wada N, Kadekawa K, Majima T, Shimizu T, Okada H, Tyagi P, Kakizaki H, Yoshimura N.

Prostaglandin is synthesized from arachidonic acid via the COX pathway in response to various physiological and pathological stimuli. Of the prostaglandins, prostaglandin E2 (PGE2) is known to be increased in urine of patients with lower urinary tract (LUT) dysfunction including interstitial cystitis/bladder pain syndrome (IC/BPS) and overactive bladder (OAB). There have also been several studies that examined the roles of PGE2 or E-series prostaglandin (EP) receptors using cystitis model animals to explore the PGE2-EP mechanism underlying IC/BPS pathogenesis. In this study, Wada and colleagues further investigated the effects of intrathecal administration of a selective EP4 receptor antagonist, ONO-AE3- 208, on bladder activity and compared the results with those of the intravesical treatment in CYP-induced cystitis rats in order to determine the site(s) of action of EP4 receptor activation that is involved in cystitis-induced bladder dysfunction. The authors found that because intravesical or intrathecal administration of EP4 receptor antagonist effectively reduced cystitis-induced bladder overactivity in a rat model, blockade of EP4 receptors at bladder and spinal cord levels could have a therapeutic potential for reducing bladder symptoms in patients with IC/BPS.

Abstract 226

TRPM7 CONTRIBUTES TO INTERCELLULAR JUNCTION FORMATION IN THE UROTHELIUM – POSSIBLE LINK TO THE PATHOPHYSIOLOGY OF INTERSTITIAL CYSTITIS

Watanabe M, Suzuki Y, Uchida K, Miyazaki N, Murata K, Matsumoto S, Kakizaki H, Tominaga M.

Transient receptor potential melastatin 7 (TRPM7) is a calcium-permeable non-selective cation channel with a unique kinase domain in its C-terminal region (1. Previous studies suggest its involvement in cellular and total body magnesium homeostasis as well as cancer cell adhesion and migration in vitro. In the urinary bladder, functional expression of TRPM7 has been reported in the urothelium. However, its physiological significance in vivo still remains unknown. The purpose of this study was to reveal the physiological role of TRPM7 in mouse urothelium in vivo. The results suggest that TRPM7 is involved in the formation of intercellular junctions in mouse urothelium. The immature intercellular junctions in the urothelium of Trpm7 KO mice might lead to a disruption of barrier function resulting in an inflammation which may affect voiding behavior in vivo. The authors report that to their knowledge, this is the first study that demonstrates Trpm7 KO mice exhibit immature intercellular junctions in vivo. Since the increased permeability of the urothelium that causes hypersensitive bladder afferent nerves and a significant decrease in voided volume is a common pathogenesis of interstitial cystitis, they believe that their Trpm7 KO mice may serve as a good animal model for interstitial cystitis.

Abstract 228

THE THERAPEUTIC EFFICACY OF HUMAN UMBILICAL CORD BLOOD-DERIVED MESENCHYMAL STEM CELLS (UCB-MSCS) ON KETAMINE INDUCED CYSTITIS

Kim A, Song M, Yu H Y, Yoon S J, Lim J, Shin D, Choo M.

Ketamine use as a recreational drug is on a rapid increase in young people. Many reports have shown that long-term ketamine abuse is liable to lead to lower urinary tract symptoms that resemble interstitial cystitis (IC). IC is a disease characterized by severe chronic pelvic pain with frequency, urinary urgency, and nocturia in the absence of bacterial infection or other diseases. This study from Korea evaluated the therapeutic effect of human umbilical cord blood derived mesenchymal stem cells (UCB-MSCs) in a ketamine induced cystitis (KC) rat model. The authors found that stem cell therapy could be a valuable treatment option for painful bladder conditions such as ketamine induced interstitial cystitis.

Abstract 234

THE EFFECT OF INTRAVESICAL LIPOSOME-BASED NGF ANTISENSE THERAPY ON BLADDER OVERACTIVITY AND NOCICEPTION IN A RAT MODEL OF CYSTITIS INDUCED BY HYDROGEN PEROXIDE

Majima T, Tyagi P, Dogishi K, Kadekawa K, Kashyap M, Wada N, Takai S, Shimizu T, Gotoh M, Chancellor M, Yoshimura N.

Nerve growth factor (NGF) has been proposed to be an important mediator for inducing hyperexcitability of afferent pathways that contributes to pain and storage symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). A previous clinical study indicated that systemic application of NGF monoclonal antibody significantly reduced pain/urgency in IC/BPS patients, but its systemic adverse events such as paresthesia and hyperesthesia were a critical issue. Therefore, the site-specific reduction of NGF would be desirable to reduce the intrinsic toxicity from systemic blockade of NGF. The authors' previous study demonstrated that intravesical liposome-based NGF antisense therapy significantly improved bladder overactivity in a rat model of acute cystitis induced by intravesical application of acetic acid. However, it still remains unclear whether local NGF antisense therapy has a chronic effect. Therefore, they investigated the effect of intravesical liposome-based NGF antisense therapy on bladder overactivity and nociceptive behaviour in a rat model of chronic cystitis induced by hydrogen peroxide (HP). Their results indicate that: (1) intravesical hydrogen peroxide instillation, which induces bladder inflammation up to 7 days after the instillation, elicit frequent urination shown by reduced ICI, and enhanced bladder pain sensitivity shown by increased freezing behaviour, which are associated with increased expression of NGF mRNA and protein as well as TRPV1 mRNA in the bladder mucosa and bladder afferent pathways and (2) intravesical liposome-based NGF antisense therapy induces a reduction in the NGF mRNA and protein expression in the bladder mucosa and bladder afferent pathways, which results in the improvement of bladder pain behaviour and frequent urination induced by hydrogen peroxide-induced chronic cystitis. According to the authors, intravesical liposome-based NGF antisense therapy could be a novel treatment that can avoid systemic adverse events for hypersensitive bladder disorders such as IC/BPS, in which NGF has been implicated as an important mediator for inducing afferent sensitization.

Abstract 235

BAY 58-2667, A SOLUBLE GUANYLYL CYCLASE ACTIVATOR, PREVENTS CYCLOPHOSPHAMIDE INDUCED CYSTITIS IN MICE.

Oliveira M, Antunes E.

Cyclophosphamide (CYP) is commonly used as an experimental model for the investigation of IC because of its similarity with the human disease. Studies demonstrate that extensive oxidative stress during inflammation compromise bladder function by impairing the nitric oxide (NO)-soluble guanylylcyclase (sGC)-cGMP signalling. This study with mice aimed to evaluate whether sGC activation by BAY 58- 667 prevents CYP-induced cystitis. The authors found that CYP caused pronounced urinary bladder inflammation and bladder overactivity. BAY 58-2667 pre-treatment prevented significantly these alterations, ameliorating the bladder dysfunction. They concluded that activation of sGC-cGMP signaling pathway by sGC activators confers a protective effect in CYP-induced cystitis, providing a potential therapeutic target for IC.

Abstract 236

GAG-REPLENISHMENT: PROTECTING THE UROTHELIUM FROM CHRONIC DAMAGE.

Rozenberg B, Janssen D, Jansen K, Schalken J, Heesakkers J.

Urothelium has a very low permeability which protects the deep layers of the bladder wall from irritant urine solutes. The first line of defense, the glycosaminoglycans (GAG) layer, is believed to be compromised in patients with bladder pain syndrome, enabling substances such as urea and potassium to leak into the bladder wall and cause inflammation leading to irritative symptoms. This is the base for the rationale behind GAG-replenishment therapies such as intravesical instillations with chondroitin sulfate (CS). In this study from the Netherlands, for the first time the urothelial barrier function is objectively measured before and after GAG-replenishment. The urothelium was damaged repeatedly in order to simulate a more chronic situation. In addition to functional barrier measurements, the effects were visualized using scanning electron microscopy (SEM). Primary porcine urothelial cells were cultured on membranes which made it possible to measure the transepithelial electrical resistance (TEER) which is a measure for barrier function. The barrier recovered partially in both damaged groups while in the control group TEER remained stable Nevertheless, the group in which additional CS was instilled showed a significantly faster recovery. SEM showed a different appearance of the urothelium after CS instillation. The authors concluded that the urothelial barrier is able to recover from repetitive injury which enables the model to be used in a more chronic situation. Moreover, it shows that in repeatedly damaged urothelium, CS has an advantageous effect on barrier recovery.

Abstract 291

PREVALENCE, AWARENESS, AND UNDERSTANDING OF PELVIC FLOOR DISORDERS IN ADOLESCENT AND YOUNG WOMEN

Parden A, Hoover K, Ellington D, Gleason J, Burgio K, Richter H.

Pelvic floor disorders (PFDs), including urinary incontinence (UI), fecal incontinence (FI), and pelvic organ prolapse (POP), affect a large proportion of the population, represent an enormous burden on health care cost, and impact the quality of life of women. Prevention of these conditions requires an understanding of what young women know about these conditions before they actually occur. There is a paucity of data evaluating younger women's knowledge-base of PFDs and prevalence of pelvic floor symptoms. The primary aims of this study were to determine the prevalence, awareness, and understanding of female pelvic floor disorders among women age 19-30. According to the authors, this information may be used to help plan educational strategies in adolescents regarding factors associated with the development of PFDs. Primary prevention for the development of PFDs needs to be more fully addressed.

Abstract 441

IMMUNOGLOBULIN E PLAYS AN IMPORTANT ROLE IN THE PATHOGENESIS OF BLADDER PAIN SYNDROME -- AN IMMUNOHISTOCHEMICAL STUDY OF PAINFUL BLADDERS

Jhang J, Jiang Y, Kuo H.

Jhang and colleagues from Taiwan note that researchers have recently started to use the term bladder pain syndrome (BPS) to describe cases with painful urinary symptoms in several diseases with different clinical characteristics. However, the pathogenesis difference between different diseases of BPS is still unclear. The authors previously found elevated serum immunoglobulin E (IgE) in the patients with ketamine related cystitis (KC). This study was designed to investigate the role of IgE in the pathogenesis of different BPS diseases. They found that bladder IgE expression is significantly abnormally increased in the patients with KC ulcer IC. IgE mediated inflammation might participate in the pathogenesis in at least part of BPS patients.

Abstract 442

ACTIVATION OF TOLL LIKE RECEPTOR 7 INDUCES CYSTITIS AND FACILITATION OF BLADDER PAIN AND MECHANO-SENSATION IN MICE

Ichihara K1 Aizawa N, Sugiyama R, Ito H, Kamei J, Akiyama Y, Masumori N, Homma Y, Igawa Y.

Toll like receptors (TLRs) function as sentinels, alerting the innate immune system in the presence of threatening microbial invasion. Among them, TLR7 is mainly expressed in neural and inflammatory cells, but also in the human and mouse bladder urothelium, and responsible for the sensation of pain and induction of inflammation. It has been proposed that TLR7 is involved in some auto-immune diseases such as systemic lupus erythematosus and Sjögren's syndrome, well-known diseases associated with interstitial cystitis. Ichihara and colleagues from Japan hypothesize that TLR7 may have a pathophysiological role in the development of bladder pain and interstitial cystitis. However, to date, there has been no report about the role of TLR7 in the bladder sensory and inflammatory disorders. Therefore, they investigated the effects of TLR7-activation provoked by intravesical instillation of its selective agonist, loxoribine (LX), on nociception, mechano-sensation and histology of the bladder in mice. Their results indicate that activation of the bladder TLR7 can induce cystitis and facilitation of the bladder mechano-sensory and nociception pathways in mice.

Abstract 443

F16357, A NOVEL PAR-1 ANTAGONIST IMPROVES URODYNAMIC PARAMETERS AFTER INFLAMMATION IN A NEW MODEL OF RAT CYSTOMETRY BASED ON BLADDER SENSATION.

Monjotin N, Farrié M, Le Grand B, Vergnolle N, Gillespie J, Junquero D.

The main roles of urinary bladder are the storage of urine and its voiding at a socially convenient moment. Storage properties can be disturbed in many pathological situations, among them cystitis and painful bladder syndrome. Proteases released during bladder inflammation play a key role in the urinary system and hyperalgesia, and the deficiency of protease-activated receptor-1 reduced bladder in inflammation. The aim of this study was (i) to characterize a new model of cystometry by telemetry in conscious rats, (ii) to determine whether the animal decision plays a role in the initiation of voiding in physiological, inflammatory and painful conditions, (iii) to evaluate bladder effects of a PAR-1 antagonist under physiological and inflammatory

conditions. The authors are of the opinion that their telemetric model is likely to be more accurate than previously described conscious conventional cystometry, and allows the evaluation of compounds which could modulate the voiding pattern by targeting the detrusor contractility and the sensitive afferences. Furthermore, this model addresses some key criteria of human Interstitial Cystitis and Bladder Pain Syndrome such as urgency, pain or pressure. In these conditions, the novel PAR-1 antagonist F16357 seems to be a good candidate for IC/PBS treatment.

Abstract 444

BLADDER PAIN IN BPS/IC MAY RESULT FROM AN EXAGGERATED RESPONSE OF TRPV1 AND ENHANCED UROTHELIAL ATP RELEASE INDUCED BY CHRONIC ADRENERGIC

Matos R, Cordeiro J, Igawa Y, Cruz F, Charrua A.

Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) patients present increased activity of sympathetic nervous system. In addition, BPS/IC bladders overexpress TRPV1 and produce increased amounts of ATP [1]. In an animal model of chronic adrenergic stimulation, it was observed that chronic administration of phenylephrine (PHE) induced bladder pain. [2]. Whether this is a mere coincidence or results from a functional cross-talk between the adrenergic system and bladder nociceptive pathways like TRPV1 and ATP are unknown. In the present work, Matos and colleagues from Portugal postulate that the disproportionate intensity of bladder pain observed during normal bladder filling in BPS/IC patients is the consequence of TRPV1 sensitization and of the enhancement of ATP release from urothelial cells in response to innocuous stimuli caused by chronic adrenergic stimulation. There are two pain mechanisms attributed to BPS/IC patients, one involving the purinergic pathway and another involving TRPV1 receptor. In the present work the authors show that both of these mechanisms can be sensitized/activated through a process mediated by alpha 1A adrenoceptor activation. TRPV1 is an important pain pathway and TRPV1 expression is increased in BPS/IC patients. In addition, increased urothelial ATP release is typically observed in BPS/IC patients, which might activate P2X3 nociceptors coursing the bladder suburothelium. They concluded that alpha 1A-mediated adrenergic overstimulation sensitizes TRPV1 and increases ATP release from urothelial cells and that both mechanisms may contribute to the disproportionate pain response to innocuous stimulation seen in BPS/IC patients during innocuous bladder filling.

Abstract 463

THE CORRELATION OF URINE NERVE GROWTH FACTOR LEVELS WITH BLADDER NERVE STAINING CONCENTRATION AND SYMPTOM SCORE SEVERITY IN INTERSTITIAL CYSTITIS PATIENTS

Tonyali S, Ates D, Akbiyik F, Ergen A.

In this study, Tonyali and colleagues aim to assess the role of nerve fibers and nerve growth factor (NGF) in IC etiopathology and to demonstrate if there is a correlation between bladder nerve staining concentration, NGF and symptom severity. Thus, there might be no reason for unnecessary, expensive and troublesome tests and treatments. They report that this is the first study in the literature showing the importance of nerve fiber staining and urine NGF levels in IC patients and their effects on symptom and problem index scores. The role of nerve system and related neuropeptides and neurotrophins in IC pathogeneses cannot be ruled out. NGF could be use as a useful biomarker both for the diagnosis and assessment of symptom and problem severity. Because of the low patient number and limited current evidence, more large, controlled and randomized trials are mandatory.

Abstract 477

ITALIAN VALIDATION OF PELVIC PAIN AND URGENCY/FREQUENCY PATIENTS SYMPTOMS SCALE (PUF) QUESTIONNAIRE

Filocamo M, Natale F, Andretta E, Ales V, Maruccia S, Mariotti G, Costantini E, Villari D.

The purpose of this study from Italy was to translate the English-written PUF scale into an Italian version that objectifies the degree of the symptoms in order to diagnose IC/PBS and to assess the linguistic validation of the Italian version in a population of IC/PBS patients versus healthy volunteers. The authors aimed for domestic researchers to be able to use the Italian version in clinical research and in the clinical treatment of domestic IC/PBS patients. They are of the opinion that the Italian version of PUF questionnaire is reliable and has good discriminatory ability for assessment in patients with IC/PBS. The PUF score correlates well with symptom severity as well as endoscopic abnormalities and bladder capacity in patients with IC/PBS.