Purinergic P2X7 receptors as therapeutic targets in interstitial cystitis/bladder pain syndrome; key role of ATP signaling in inflammation

Zhinoos Taidi1, Kylie J. Mansfield2, Lucy Bates3, Hafiz Sana-Ur-Rehman1, Lu Liu1*  
1School of Medical Sciences, The University of New South Wales, Sydney NSW 2052, Australia  
2School of Medicine, University of Wollongong, Wollongong, NSW 2522, Australia  
3Westmead Hospital, Westmead, NSW 2145, Australia  
*Corresponding author: Lu Liu, Email: lu.liu@unsw.edu.au  
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ABSTRACT  
Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic lower urinary tract condition. Patients with IC/BPS suffer from debilitating pain and urinary urgency. The underlying etiology of IC/BPS is unknown and as such current treatments are mostly symptomatic with no real cure. Many theories have been proposed to describe the etiology of IC/BPS, but this review focuses on the role of inflammation. In IC/BPS patients, the permeability of the urothelium barrier is compromised and inflammatory cells infiltrate the bladder wall. There are increased levels of many inflammatory mediators in patients with IC/BPS and symptoms such as pain and urgency that have been associated with the degree of inflammation. Recent evidence has highlighted the role of purinergic receptors, specifically the P2X7 receptor, in the process of inflammation. The results from studies in animals including cyclophosphamide-induced hemorrhagic cystitis strongly support the role of P2X7 receptors in inflammation. Furthermore, the deletion of the P2X7 receptor or antagonism of this receptor significantly reduces inflammatory mediator release from the bladder and improves symptoms. Research results from IC/BPS patients and animal models of IC/BPS strongly support the crucial role of inflammation in the pathophysiology of this painful disease. Purinergic signaling and purinergic receptors, especially the P2X7 receptor, play an undisputed role in inflammation. Purinergic receptor antagonists show positive results in treating different symptoms of IC/BPS.

Keywords: ATP, bladder pain syndrome, inflammation, interstitial cystitis, purinergic receptors

INTRODUCTION  
Interstitial cystitis (IC) is a chronic lower urinary tract condition. IC is also called bladder pain syndrome (BPS) [1] and was previously referred to as painful bladder syndrome (PBS) [2]. All three terms are considered to refer to the same condition. The term “IC/BPS” has been widely used in the literature and will be used here. The underlying etiology of IC/BPS is unknown and as such the current therapeutic approaches are mostly symptomatic with no real cure available. To date, many theories have been proposed to describe the etiology of IC/BPS, but this review focuses on the role of inflammation in this disease. Since Burnstock introduced purinergic signaling in the 1970s, many different roles of purinergic receptors have been revealed but one of the most recent major topics is their role in the process of inflammation. Thus, this review will discuss the possible involvement of purinergic receptors and ATP as their signaling molecule in the pathophysiological development of IC/BPS with particular focus on the P2X7 receptor, given that recent studies have revealed that P2X7 receptor is a potent stimulant of inflammation and immune response, which makes this receptor a potential target for anti-inflammatory treatment.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME  
IC/BPS is a chronic lower urinary tract condition characterized by pain perceived to be associated with the bladder filling [3]. The main
The effectiveness of the currently available therapies is low and there is urgency, for the available therapies. For example, two clinical trials to provide scientific evidence of efficacy concluded that there are insufficient data to support the use of certain therapies for IC/BPS. In addition to these oral medications, dimethyl sulfoxide (DMSO), heparin and lidocaine have been used topically to decrease pain by instilling into the bladder lumen in IC/BPS patients. Pentosan polysulfate sodium (PPS), which forms a protective layer on the bladder lining, as a last resort, the immunosuppressant agent cyclosporine A and also medications, a variety of different agents have been used with variable success in IC/BPS patients. These include the tricyclic antidepressant amitriptyline, antihistamine/anti-anxiety medication hydroxyzine, and as a last resort, the immunosuppressant agent cyclosporine A and also pentosan polysulfate sodium (PPS), which forms a protective layer on the bladder lining. Evidence of inflammation in biopsy samples from IC/BPS patients is part of the diagnosis of the disease although routine biopsies are not recommended for IC/BPS patients. Based on the guidelines of American Urological Association and Canadian Urological Association, there is no urinary tract infection (UTI) at the time of diagnosis but up to 50% of IC/BPS patients might have a history of previous UTI.

CURRENT TREATMENT OPTIONS
The current therapeutic approaches for IC/BPS patients are mostly symptomatic with no real cure identified. The current treatments include behavioral therapy, oral medications, intravesical treatments as well as surgical treatments. Behavioral therapy involves modifying daily fluid intake, clothes, food and sexual behavior with the aim of reducing the likelihood of triggering symptoms. In terms of oral medications, a variety of different agents have been used with variable success in IC/BPS patients. These include the tricyclic antidepressant amitriptyline, antihistamine/anti-anxiety medication hydroxyzine, and as a last resort, the immunosuppressant agent cyclosporine A and also pentosan polysulfate sodium (PPS), which forms a protective layer on the bladder lining. In addition to these oral medications, dimethyl sulfoxide (DMSO), heparin and lidocaine have been used topically to decrease pain by instilling into the bladder lumen in IC/BPS patients either separately or in combination. Intravesical therapy by injecting botulinum toxin A (BTX-A) into the bladder wall of IC/BPS patients has shown some improvement in pain, voiding frequency and patients’ quality of life.

The effectiveness of all these therapies, regardless of being systemic or topical, is still under consideration. A recent meta-analysis on intravesical therapy for IC/BPS concluded that there are insufficient well-controlled clinical trials to provide scientific evidence of efficacy. The clinical trials that have been conducted have demonstrated fairly low response rates, with regard to improvement in bladder pain and urgency, for the available therapies. For example, two clinical trials of intravesical PPS in IC/BPS patients showed 34% [23] and 40% response rates [24], while intravesical DMSO reported response rates of 30% [25] and 14% [26], which are not significantly different from the placebo response rate of ~20% [23]. These studies demonstrate that the effectiveness of the currently available therapies is low and there is a need for the development of new and effective treatment options.

CLINICAL EVIDENCE OF INFLAMMATION IN IC/BPS

Observations from cystoscopy and biopsy samples from IC/BPS patients
The importance of inflammation in the pathophysiology of IC/BPS can be clearly seen on cystoscopy. The most common finding on cystoscopy of patients with IC/BPS is mucosal damage and hemorrhages. IC/BPS is diagnosed at cystoscopy when the bladder has been filled to its maximum capacity (at a pressure of 80–100 cm H₂O). In IC/BPS patients mucosal splitting or glomerulations (petchelial hemorrhages) are seen in a minimum of 3 quadrants, with 10 per quadrant. It should be noted that two types of IC/BPS have been defined based on cystoscopy findings, that are: IC/BPS with or without Hunner ulcer. Hunner ulcers, visualized on cystoscopy, are areas away from the bladder trigone that are either inflamed areas of the mucosa that may have small vessels joining each other at one central point, or may appear pale, non-blanching if in the chronic state. These ulcers can easily split open with bladder distension which causes bleeding. The presence or absence of Hunner ulcer in IC/BPS patients is believed to have an important role in symptom variations, differences in therapeutic success and the level of pain, especially the pain related to bladder distension. Mucosal splitting, glomerulations and Hunner ulcers are all signs of mucosal damage.

The role of inflammation in mucosal damage is evident in biopsies collected from IC/BPS patients. Recent studies have emphasized inflammation as the common cause of different types of urinary tract dysfunction. In biopsies collected from IC/BPS patients, it has been shown that inflammation is associated with disruption to the urothelial cell layer, increased density of sub-urothelial afferent nerve fibers, and infiltration of inflammatory cells such as mast cells. However, it is unknown whether inflammation causes damage to the mucosa or it is the consequence of mucosal damage.

Urothelial changes
There are many changes to the urothelial cells in patients with IC/BPS. The urothelium of IC/BPS patients is thinner, usually only 1 or 2 cells thick, compared to the urothelium from normal bladders which is approximately 5 cells thick. Also in IC/BPS patients, the urothelium does not include a distinct layer of umbrella cells and urothelial cell apoptosis has been described. These findings suggest that disruption to the structure of the urothelium is a feature of the pathophysiology of IC/BPS. Associated with the changes in the urothelial structure is the disruption to the permeability function of the urothelium. Although the main role of bladder urothelium is thought to provide a barrier which is impermeable to all urinary solutes, reduced urothelial barrier function has been observed in patients with IC/BPS. A recent study in rats has shown altered expression and function of paracellular tight junctions in the urothelium may trigger bladder inflammation and promote cystitis.

On the luminal side of the bladder wall, a glycosaminoglycan (GAG) layer, a highly hydrated barrier surface, acts as the first protecting layer against urinary toxins and solutes. This GAG layer is made up of hyaluronate, chondroitin sulfate, heparin sulfate, keratin sulfate and dermatan sulfate. Deficiency of the luminal and basal chondroitin sulfate proteoglycan layers has been demonstrated in bladder biopsies from IC/BPS patients, and therefore it was proposed that GAG layer deficiencies may be associated with permeability changes in IC/BPS.
patients [44,45]. However, other studies have shown that although GAG layer can be a barrier for the movement of microorganisms, its contribution to the urothelial permeability is unclear [46,47] (for reviews see [48,49]).

GAG layer replenishment is one of the main therapeutic strategies in the treatment of IC/BPS. The aim of the intravesical instillations of PPS, DMSO and heparin is to promote the recovery of the damaged GAG layer. PPS, which is similar in structure to the natural GAG, is believed to replenish the protective covering of the urothelium. DMSO is thought to reduce inflammation and act as an analgesic and heparin, which is a sulfonated GAG, has both anti-inflammatory and surface replenishing properties [50]. However, as mentioned previously, the effectiveness of these two therapies is low [24,26], which may be explained by the observations that the GAG layer has no influence on urothelial permeability [46,47].

Other urothelial associated proteins also contribute to the permeability barrier. These include the uroplakins that form a covering over the urothelial luminal surface [51] and the tight junction proteins that bind the urothelial cells together [42]. In patients with IC/BPS, there is an absence of the tight junction protein zona occludens-1 (ZO-1), and also there are deficiencies in the expression of uroplakin and E-cadherin [40]. The change in ZO-1 expression may be associated with the increased permeability of the bladder urothelium in IC/BPS patients [41]. It is highly likely that both the decreased thickness of the urothelial cell layer and the increased urothelial permeability are associated with the symptoms that patients experience such as pain and urgency. Both of these symptoms have negative effects on the quality of life in these patients.

**Increased inflammatory mediators**

The core role of inflammation in the etiology of IC/BPS has been investigated in many studies. The initial evidence for inflammation in biopsies from patients with IC/BPS was increased mast cell counts. The increase in mast cells in biopsies from patients with IC/BPS compared to normal control was described in the detrusor muscle layer [5] and also in the sub-urothelial layer [52,53]. Interestingly, the increased number of mast cells in the sub-urothelial layer was localized to the areas underlying ulcers in patients with IC/BPS [52]. This same study showing localized mast cells within the urothelial layer has also demonstrated the presence of mast cells in the intravesical fluid [52].

Higher counts of other inflammatory cells such as neutrophils and eosinophils have been also reported in the urine samples from IC/BPS patients [54]. Neutrophils make up approximately 70% of white blood cells and have a well-known contribution to the acute inflammatory response [55]. Eosinophils, on the other hand, are important regulators of local inflammatory response and their accumulation is linked to many inflammatory diseases [56]. Many studies have linked the damaged urothelium to activation and stimulation of the inflammatory cells in the bladder of IC/BPS patients which can trigger the release of other inflammatory mediators [57-61].

In IC/BPS patients, there is also an increase in the concentration of inflammatory mediators such as histamine, which is released following mast cell activation. Histamine has been found in the urine samples from IC/BPS patients [62,63]. Other inflammatory mediators are also increased. For instance, IC/BPS patients have a higher expression of inducible nitric oxide (NO) synthase mRNA in the urothelium [53,64], and in the sub-urothelial macrophages [64]. There is also a significant increase in the luminal concentration of NO [64]. NO is a signaling molecule that is believed to have an anti-inflammatory effect in the normal condition, but its over production in pathophysiological conditions can lead to it acting as a pro-inflammatory mediator [65]. Gene expression of other inflammatory mediators is also increased in patients with IC/BPS. These include genes for FGFl7, CCL21 [66], IL-6, IL-10 and IL-17A [53]. At a protein level, an upregulation of urinary IL-17A [53] which is a mediator for pro-inflammatory responses [67,68], and urinary IL-6 [63], which is mainly produced in the case of tissue injury and infections [69], has been reported.

The increases in inflammatory mediators are not just limited to the bladder, as an enhanced plasma IL-6 [70] has also been detected in IC/BPS patients. Another study shows higher levels of C-reactive protein and pro-inflammatory cytokines/chemokines, e.g., IL-1β, IL-6, TNF-α and IL-8 in the serum of patients with IC/BPS compared to controls [71]. An interesting study demonstrated elevated serum levels of MIG/CXCL9, IP-10/CXCL10 and I-TAC/CXCL11 in IC/BPS patients. Elevated CD4+ T cells, mast cells, natural killer (NK) cells, and NKT cells have been shown at the systemic and mucosal sites in a mouse model of cyclophosphamide induced hemorrhagic cystitis [72]. Also, in a cyclophosphamide model of IC/BPS, the infiltration of inflammatory cells such as macrophages and neutrophils has been described along with an increase in TNF-α and IL-1β in the urothelial and sub-urothelial layer of the bladder [73]. All these data strongly support the role of inflammation in the pathophysiology of IC/BPS. Increased densities of inflammatory cells in the bladder have been described and increased concentrations of inflammatory mediators are believed to contribute to the etiology of the disease.

**Role of sensory nerve fibers**

As mentioned above, the key symptoms associated with IC/BPS are pain and urgency. Bladder sensations, such as a frequent need to void, pain and urgency, are carried on sub-urothelial afferent nerves. Since the 1990s, it has been known that the density of nerve fibers was increased in patients with IC/BPS, compared to normal controls [74]. The increase in mast cells and histamine in bladder washings has been associated with an increase in nerve fibers in both the sub-urothelial layer and in the detrusor muscle of IC/BPS patients [75]. It is also likely that the increased density of nerves fibers is related to increased levels of nerve growth factor seen in the serum [71], biopsies [36] and urine [76] of IC/BPS patients. Urinary nerve growth factor levels also correlate with symptoms of urgency [76] and it is believed that the increased nerve density may explain the symptoms of both pain and urgency.

In IC/BPS patients, a specific increase in the sensory afferent nerves located in the sub-urothelial space has been reported [36,38,76]. There is a correlation between the expression of afferent nerves that are immunoreactive for TRPV1 and the pain and urgency scores in IC/BPS patients [36] and a correlation between the density of PGPP9.5-immunoreactive nerve fibers and inflammation severity in IC/BPS patients [36]. The concentration of substance P containing afferent sensory nerves is also increased in the sub-urothelial space [38] of IC/BPS patients. Substance P is a neuropeptide that plays an important role in inflammation and is overexpressed in many inflammatory conditions [77-84]. One study has suggested that an increase of sub-urothelial nerve fibers is specifically in ulcerative IC/BPS but not seen in biopsies from patients with non-ulcerative IC/BPS [75]. These studies indicate that it is likely that the enhanced pain felt by patients with IC/BPS during
bladder filling is related to the increased density of afferent nerves in the sub-urothelial layer. Increased ATP release in IC/BPS patients also seems to have a role in sensitization of afferent nerves, which will be discussed in detail in the next section.

Overall there is much evidence of inflammation in IC/BPS patients. This includes macroscopic evidence of bleeding and ulceration seen on cystoscopy. Biopsies from these patients revealed enhanced nerve density, infiltration of inflammatory cells and urothelial damage. In addition, urine and blood samples taken from IC/BPS patients have shown increased levels of pro-inflammatory mediators. The evidence for a significant role of inflammation to the pathophysiology of IC/BPS is summarized in Figure 1.

Figure 1. A summary of inflammation evidence based on the results of different studies which have been performed on IC/BPS patients and their biopsy, urine and blood samples. †indicates increased; *indicates infiltration.

ATP AS A SIGNALING MOLECULE FOR BLADDER PAIN AND URGENCY

In the early 1970s, Burnstock first reported the role of purinergic nerves as a non-adrenergic non-cholinergic nervous system, with ATP as its signaling molecule [85]. The purinergic system consists of two main groups of receptors; P1 and P2 receptors. P1 receptors, which are also known as adenosine receptors, have been shown to be expressed in urinary bladder where they exert an inhibitory action during the micturition reflex and inhibit cholinergic neurotransmission [86-89]. Purinergic P2 receptors are further divided into two sub-classes of P2Y and P2X. P2Y receptors, which respond preferentially to ADP and UTP, are G-protein coupled receptors and P2X receptors, responding to ATP and P2X. P2Y receptors, which respond preferentially to ADP and UTP, are G-protein coupled receptors and P2X receptors, responding to ATP and P2X. P2Y receptors, which respond preferentially to ADP and UTP, are G-protein coupled receptors and P2X receptors, responding to ATP and P2X.

There are eight subtypes of the human P2Y receptors. The expression of P2Y1 [96,100], P2Y2 [96,100,101], P2Y4 [100,101], P2Y6 [102,103] and P2Y11 receptors [96] has been shown in the urothelium layer of the urinary bladder of cat [100], rat [101-103] and human [96], using RT-PCR [96], western blotting [101] and immunostaining techniques [100,102,103]. Expression of P2Y2, P2Y4 and P2Y6 have also been observed in guinea pig suburothelial myofibroblasts by immunostaining [104].

Under the normal condition, the sub-urothelial afferent nerves are activated by ATP released from the urothelium [105,106] in response to stretch of the urothelial cells [99,107-111]. Several mechanisms for ATP release have been identified, including both vesicular and non-vesicular pathways [112,113]. Vesicular ATP release is mediated by the exocytosis of ATP-enriched vesicles [112] from both neurons upon action potential [114,115] and non-excitatory cells such as urothelial cells [111].

ATP release from the urothelium is not just occurring through vesicles but also involves the activation of channels and pores in the urothelial cell membrane. One such mechanism involves pannexin channels [116]. Pannexin channels are closed under resting conditions. However they will be activated by ligand binding to membrane receptors such as ATP binding to P2X7 receptor [117]. It has been shown that pannexin-1 channel and P2X7 receptor are co-expressed in urothelial cells [118] and binding of ATP to P2X7 receptor triggers the opening of the pannexin pore [118] which causes a further release of ATP. Similarly, ATP release

[99]. P2X7 receptor immunoreactivity is abundant on both smooth muscle and urothelium [95].
from the urothelium can also be triggered by the activation of P2Y receptors [119,120]. Also, after its cellular release, ATP can be rapidly metabolized to ADP, AMP and adenosine and activate other purinergic receptors to mediate smooth muscle relaxation or contraction [121-124].

ATP released from the urothelium, in response to stretch, is an important signaling molecule that modulates the sensation of fullness felt in the bladder and mediates the voiding reflex viaafferent sensory nerves [125,126]. However, an analysis of single unit pelvic afferent activities has shown that ATP is involved in both non-nociceptive (physiological) and nociceptive (painful) signal transduction [126], supporting the notion that in the urinary bladder, both high and low threshold afferent nerve fibers are sensitive to ATP. Therefore, one of the primary roles of ATP following its release from the urothelium is to activate sensory afferent nerves. The process is mediated by purinergic receptors [92,95,127]. Agonists of purinergic P2X receptors, ATP and α, β-meATP have been shown to trigger bladder afferent nerve activity which was attenuated in P2X3 knockout mice and by P2X3 antagonists [99], demonstrating that P2X3 receptors are responsible for ATP elicited responses on afferent nerves. ATP release has been shown to be increased in the bladder of both patients with IC/BPS [107,108] and animal models of IC/BPS [111]. In patients with IC/BPS, urinary levels of ATP were significantly higher than that of controls [107]. In addition, stretch induced release of ATP was enhanced in bladder strips [128] and urothehial cells from patients with IC/BPS [108]. Similar to the reports in human IC/BPS, a significant elevation in stretch-evoked ATP release has been demonstrated in a feline model of IC/BPS [111] and in cyclophosphamide-induced chronic (hemorrhagic) bladder inflammation in rats [129]. The high level of ATP and other urinary contents may diffuse through the leaky urothelium to sensitize bladder afferents, causing pain sensation and stimulating voiding, which are the typical symptoms of IC/BPS [130].

Blocking the release of ATP has shown promising results as a potential treatment for IC/BPS patients to improve the symptoms of pain, urgency and frequency. As an example, BTX-A has been used with some success in the treatment of IC/BPS [19-21]. BTX-A was shown to inhibit the stretch-mediated release of ATP from the inflamed rat bladder [129] and have anti-pain effects in IC/BPS patients [131]. Studies on the effect of BTX-A in IC/BPS has been reviewed in Chu et al. [132]. BTX-A doesn’t target purinergic receptors directly, but it can potentially inhibit the activation of the purinergic receptors by blocking the release of ATP. It is well accepted that afferent nerve density and ATP release are increased in patients with IC/BPS. Therefore, targeting these pathways might influence the symptoms of pain, urgency and frequency experienced by IC/BPS patients. There have been some studies to examine these possibilities. Studies in P2X2 and P2X3 knockout mice have demonstrated marked urinary bladder hyporeflexia with increased voiding volume, reduced voiding frequency and reduced response to inflammatory pain, suggesting a prominent role of P2X2 and P2X3 receptors in mechanosensory transduction and physiological voiding reflexes [106,133].

In addition, antagonists targeting these receptors have been investigated as a potential treatment for patients with IC/BPS. P2X2/3 receptor antagonist AF-219, which is metabolically stable and has oral bioavailability, has recently been used as a therapeutic agent in IC/BPS patients with improvement in both pain and urinary urgency symptoms in treated patients [134]. In a model of cyclophosphamide-induced cystitis in rats, signs of bladder overactivity such as contraction and reduced micturition volume have been shown to be significantly improved by A-317491, a selective P2X3 receptor antagonist [135]. This antagonist has also demonstrated outstanding positive effects in a rat model of detrusor hyperreflexia, including reduced frequency of voiding and inhibition of non-micturition bladder contractions [136]. However, as mentioned previously, P2X2 and P2X3 are not the only purinergic receptors present in the urinary bladder. Other P2X receptors have also been localized within the urinary bladder [92-95].

**P2X7 PURINERGIC RECEPTOR—A MODULATOR OF INFLAMMATION**

The P2X7 receptor is of particular interest in IC/BPS as this receptor has a possible role in inflammation [137]. P2X7 receptors have been detected in both, urothelium and detrusor muscle cells [92-95]. However, the definitive expression profile of this receptor, especially in the bladder of IC/BPS, still needs to be determined. In a mouse model of hemorrhagic cystitis induced by cyclophosphamide, Martins and associates demonstrated an upregulation of P2X7 receptors in the submucosal layer [73]. P2X7 receptors are also expressed by many immune cells including macrophages, monocytes, natural killer cells, B-lymphocytes and T-lymphocytes [138]. As described previously, many immune cells are seen to be increased in the sub-urothelial space in IC/BPS patients. A few genome profiling studies have been completed in samples from IC/BPS patients and the results demonstrate an up-regulation of genes associated with inflammatory cells mainly leukocytes. Although the changes of P2X7 receptor and other purinergic receptors have not been mentioned in these studies, it cannot be ruled out that P2X7 receptor may contribute to leukocyte infiltration in these patients [139-141].

P2X7 receptors are also known to regulate the expression, and secretion of various cytokines and other inflammatory mediators including IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-2, IL-4, IL-6, IL-13, IL-18, TNF-α, NO, and superoxide anions [142]. Increases in many of these have been reported in IC/BPS patients [53,63,64,70,71]. In addition, sustained activation of P2X7 receptors is associated with apoptotic cell death [143], such as that seen in the urothelium of IC/BPS patients. Also, there have been studies implicating both ATP and P2X7 receptors in inflammatory activation which leads to the activation of the inflammatory cascade [144]. In this study, P2X7 receptors and ATP were seen to be integral to the macrophage mediated immune response against virus particles, showing the importance of the activation of P2X7 receptors in the induction of the inflammatory response [144].

Recently, many researchers have wondered if P2X7 receptor antagonists could be utilized as a treatment option for bladder diseases [73,145,146]. In 2012, Martins and associates investigated the effects of P2X7 receptor antagonists, or genetic deletion of P2X7 receptor, in cyclophosphamide-induced hemorrhagic cystitis in mice [73]. They found a decrease in the pain response in the cyclophosphamide treated animals following either pre-treatment with a P2X7 receptor antagonist or genetic removal of P2X7 receptors [73]. They also reported that the treatments led to decreased inflammatory responses and reduced edema and hemorrhage, based on macroscopic and histological assessments [73]. Also, other interesting results were observed in the models of P2X7 receptor antagonist treatment, including reduced myeloperoxidase activity and reduction in the level of IL-1β and TNF-α in bladder [73]. Myeloperoxidase is an enzyme mainly expressed in neutrophils and monocytes and plays an important role in their antimicrobial activity [147].
While the effect of P2X7 receptor antagonists in urinary bladder inflammation needs further study, there are other models of inflammation that indicate the important role of P2X7 receptors. In 2002, a selective antagonist of P2X7 receptor, oxidized ATP, was seen to have an inhibitory effect on the inflammatory pain associated with arthritis in rats [148]. The results showed that the ATP level in the inflamed tissues was reduced and the pain was relieved in oxidized ATP treated animals [148], together with a reduction in P2X7 receptor expression in both the endothelium and on peripheral nerves [148]. A study on P2X7 receptor knockout mice showed a reduction of hypersensitivity in both inflammatory and neuropathic pain models [149]. They suggested that P2X7 receptor plays a regulatory role on the production of IL-1β, which is an effective pathway in the development of pain [149].

The P2X7 receptor has also been shown to have a role in inflammatory pain in kidneys. In P2X7 receptor knockout mice there was a decrease in the number of inflammatory cells following unilateral ureteral obstruction [146]. Also, less TGF-β1, lower macrophage infiltration and reduced tubular apoptosis were observed in the P2X7 receptor knockout animals [146]. In another study, treatment with a P2X7 receptor antagonist, A438079, resulted in reduced expression of chemokines, MCP-1 and RANTES, in a model of ischemic acute kidney injury in mice [150]. Similarly, it has been demonstrated that a reduced production of cytokines, TNF and IL-1β, occurred in the colon of colitis mice treated with the P2X7 receptor antagonist A438079 [151]. These results encourage further investigations to see if P2X7 blockade or deletion has any effect on pain association with inflammation in IC/BPS.

CONCLUSION

The etiology of IC/BPS is still unknown although the importance of inflammation to the pathophysiology of this disorder is well supported. Increased levels of many inflammatory mediators are seen in IC/BPS patients and symptoms such as pain and urgency have been associated with the degree of inflammation present in IC/BPS patients. Recent evidence has highlighted the role of purinergic receptors, specifically the P2X7 receptor, in the process of inflammation. In terms of IC/BPS, the important role of these receptors has been demonstrated in cyclophosphamide-induced hemorrhagic cystitis and results strongly support the idea of the crucial role of P2X7 receptor in the development of inflammation. It has also been confirmed that genetic deletion of this receptor (in P2X7 receptor knock-out mice) or blocking it with an antagonist shows a significant reduction in inflammatory mediator release and a distinguished improvement in the symptoms. However, further studies are needed to reveal all the aspects of this process to be able to evaluate the treatment efficacy and clinical utility.

Author contributions

Taidi Z searched the literature and wrote and edited the manuscript. Sana-Ur-Rehman H wrote the manuscript. Bates L was the clinical consultant. Mansfield KJ and Liu L edited the manuscript.

References

1. Cox A, Golda N, Nadeau G, Curtis Nickel J, Carr L, et al. (2016) CUAI guideline: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. Can Urol Assoc J 10: E136-E155. doi: 10.5489/cuaej.3786. PMID: 27790294
2. Warren JW, Meyer WA, Greenberg P, Horne L, Diggs C, et al. (2006) Using the International Continence Society’s definition of painful bladder syndrome. Urology 67: 1138-1143. doi: 10.1016/j.urology.2006.01.086. PMID: 16765165
3. van de Merwe, P (Joop), Nordling J, Bouchemouche P, Bouchemouche K, Cervigni M, et al. (2007) Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 53: 60-67. doi: 10.1016/j.eururo.2007.09.019. PMID: 17900797
4. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, et al. (2002) The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol 187: 116-126. doi: 10.1067/mob.2002.125704. PMID: 12114899
5. Horn T, Holm NR, Hald T (1998) Interstitial cystitis. Ultrastructural observations on detrusor smooth muscle cells. APMS10: 909-916. PMID: 9808418
6. Bogart LM, Berry SH, Clemens QJ (2007) Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol 177: 450-456. doi: 10.1016/j.juro.2006.09.032. PMID: 17226607
7. Foster HE Jr, Hanno PM, Nickel JC, Payne CK, Mayer RD, et al. (2010) Effect of amitriptyline on symptoms in treatment naive patients with interstitial cystitis/painful bladder syndrome. J Urol 183: 1853-1858. doi: 10.1016/j.juro.2009.12.106. PMID: 20303115
8. Han E, Nguyen L, Siris L, Peters K (2018) Current best practice management of interstitial cystitis/bladder pain syndrome. Ther Adv Urol 10: 197-211. doi: 10.17157/1756287218761574. PMID: 30034539
9. van Ophoven A, Pekopuu S, Heinecke A, Hertle L (2004) A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 172: 533-536. doi: 10.1016/j.juro.2003.06.004. PMID: 21497874
10. Sairanen J, Tammela TL, Leppilahit M, Multanen M, Paananen I, et al. (2005) Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 185: 2162-2170. doi: 10.1016/j.juro.2011.03.064. PMID: 21497874
11. Forrest JB, Payne CK, Erickson DR (2012) Cyclosporine A for refractory interstitial cystitis/bladder pain syndrome: experience of 3 tertiary centers. J Urol 188: 1186-1191. doi: 10.1016/j.juro.2012.06.023. PMID: 22901569
12. Theoharides TC, Sant GR (1997) Hydroxyurea therapy for interstitial cystitis. Urology 49: 108-110. PMID: 9146011
13. Perez-Marrero R, Emerson LE, Felts JT (1988) A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 140: 36-39. PMID: 3287775
14. Parsons CL, Housley T, Schmidt JD, Lebow D (1994) Treatment of interstitial cystitis with intravesical heparin. Br J Urol 73: 504-507. doi: 10.1111/j.1464-4109.1994.tb07634.x. PMID: 8012771
15. Parsons CL, Zupkas P, Proctor J, Kozioi J, Franklin A, et al. (2012) Alkalized lidocaine and heparin provide immediate relief of pain and urgency in patients with interstitial cystitis. J Sex Med 9: 207-212. doi: 10.1111/j.1755-2571.2011.00252.x. PMID: 22082303
16. Stav K, Beberashvili I, Lindner A, Leibovici D (2012) Predictors of response to intravesical dimethyl-sulfoxide cocktail in patients with interstitial cystitis. Urology 80: 61-65. doi: 10.1016/j.urology.2012.03.030. PMID: 22748865
17. Kuo H (2013) Repeated onabotulinumtoxin-a injections provide better results than single injection in treatment of painful bladder syndrome. Pain Physician 16: E15-23. PMID: 23340540
18. Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, et al. (2006) Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: a pilot study. Eur Urol 49: 704-709. doi: 10.1016/j.eururo.2005.12.002. PMID: 16417964
19. Giannantoni A, Meairni E, Del Zingaro M, Priemetti S, Porena M (2010) Two-year Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome in patients with interstitial cystitis/painful bladder syndrome. Eur Urol 58: 1186-1191. doi: 10.1016/j.eururo.2010.02.031. PMID: 20278280
20. Barua JM, Arance I, Angulo JC, Riedl CR (2016) A systematic review and meta-analysis on the efficacy of intravesical therapy for bladder pain syndrome/interstitial cystitis. Int Urogynecol J 27: 1137-1147. doi: 10.1007/s00192-015-2890-7. PMID: 26590137
21. Sant GR, Propert KJ, Hanno PM, Burns D, Culkin D, et al. (2003) A pilot clinical trial of oral pentosan polysulfate and oral hydroxyurea in patients with interstitial cystitis. J Urol 170: 810-815. doi: 10.1016/j.juro.200008320.06212.3d.
Bladder pain syndrome (interstitial cystitis) involves a deficit of proteoglycans on the bladder urothelium. Hurst RE (2003) A deficit of proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology 48: 817-821. doi: 10.1016//j.urology.2003.03.022. PMID: 12913705

Eldrup J, Thorup J, Nielsen SL, Hald T, Hainau B (1983) Permeability and transport of sodium in biopsies from patients with interstitial cystitis. J Urol 129: 58-67. doi: 10.1016/0022-5347(83)90338-x. PMID: 6905246

Sairinen I, Leppilaiti M, Tammela T, Paananen I, Aaltoma S, et al. (2009) Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. Scand J Urol Nephrol 43: 212-219. doi: 10.1080/003655908027607130. PMID: 19137459

A prospective randomized controlled multicentre trial comparing intravesical DMSO and chondroitin sulphate 2% for painful bladder syndrome/interstitial cystitis. Int Braz J Urol 43: 134-141. Epub 2016.03.02. PMID: 28124536

Hurst RE, Fall M (1998) Clinical characteristics and features of light microscopic changes in interstitial cystitis. J Urol 143: 1118-1124. doi: 10.1016/j.juro.2014.04.099. PMID: 24813342

Fukuoka M, Hara M, Kinoshita S, Suzuki S, Takahashi K, et al. (2011) Inflammatory changes in interstitial cystitis. J Urol 184: 1214-1219. doi: 10.1016/j.juro.2010.07.024. PMID: 21700703

Eldrup J, Thorup J, Nielsen SL, Hald T, Hainau B (1983) Permeability and transport of sodium in biopsies from patients with interstitial cystitis. J Urol 129: 58-67. doi: 10.1016/0022-5347(83)90338-x. PMID: 6905246

Sairinen I, Leppilaiti M, Tammela T, Paananen I, Aaltoma S, et al. (2009) Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. Scand J Urol Nephrol 43: 212-219. doi: 10.1080/003655908027607130. PMID: 19137459

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Hurst RE, Fall M (1998) Clinical characteristics and features of light microscopic changes in interstitial cystitis. J Urol 143: 1118-1124. doi: 10.1016/j.juro.2014.04.099. PMID: 24813342

Fukuoka M, Hara M, Kinoshita S, Suzuki S, Takahashi K, et al. (2011) Inflammatory changes in interstitial cystitis. J Urol 184: 1214-1219. doi: 10.1016/j.juro.2010.07.024. PMID: 21700703

Eldrup J, Thorup J, Nielsen SL, Hald T, Hainau B (1983) Permeability and transport of sodium in biopsies from patients with interstitial cystitis. J Urol 129: 58-67. doi: 10.1016/0022-5347(83)90338-x. PMID: 6905246

Sairinen I, Leppilaiti M, Tammela T, Paananen I, Aaltoma S, et al. (2009) Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. Scand J Urol Nephrol 43: 212-219. doi: 10.1080/003655908027607130. PMID: 19137459

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Hurst RE, Fall M (1998) Clinical characteristics and features of light microscopic changes in interstitial cystitis. J Urol 143: 1118-1124. doi: 10.1016/j.juro.2014.04.099. PMID: 24813342

Fukuoka M, Hara M, Kinoshita S, Suzuki S, Takahashi K, et al. (2011) Inflammatory changes in interstitial cystitis. J Urol 184: 1214-1219. doi: 10.1016/j.juro.2010.07.024. PMID: 21700703
Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. Am J Physiol Renal Physiol 312: F1447-1454. doi: 10.1152/ajprenal.00291.2013.

Expression and localization of pannexin-1 and CALHM1 in porcine bladder and their involvement in modulating ATP release. Am J Physiol Renal Integr Comp Physiol 343: F302-310. doi: 10.1152/ajprenal.00139.2012.

Expression profiling study of Hunner’s ulcer type interstitial cystitis: an array of 40-gene model. Int Urogynecol J 21: 911-918. doi: 10.1007/s00243-010-1129-x. PMID: 20243422.

Knockdown of P2X7 receptor in bladder Urothelium reduces ATP release and protects against ischemic acute kidney injury in mice. Am J Physiol Cell Physiol 308: F1161-1171. doi: 10.1152/ajpcell.00270.2014.

Regulation of Innate and Adaptive Immunity: The Role of Myeloperoxidase. J Proteomics 81: 107-115. doi: 10.1016/j.jprot.2014.02.008.

Graft rejection is associated with an altered balance of P2X receptor expression in murine cardiac xenografts. Am J Transplant 16: 332-341. doi: 10.1111/ajt.13258.

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