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# Role of Purinergic Signaling in Voiding Dysfunction

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**Abstract** *Purinergic signaling* is a term that relates to adenosine triphosphate binding to its receptor (purinergic receptors such as P2X and P2Y subtypes). This pathway has been implicated in bladder functional disorders related to interstitial cystitis/painful bladder syndrome, neurogenic bladder secondary to spinal cord injury, lower urinary tract symptoms, diabetes, and aging. Purinergic signaling occurs at multiple sites, including the central nervous system, peripheral motor and sensory nerves, detrusor smooth muscle, and bladder urothelium. Future pharmacologic agents to treat bladder functional disorders may be able to target purinergic signaling at one or more of these sites.

**Keywords** Purinergic · ATP · Purinoceptors · Voiding dysfunction · Bladder physiology

## Introduction

The discovery that adenosine triphosphate (ATP) can act as a nonadrenergic, noncholinergic neurotransmitter opened a new avenue of study exploring the role for ATP (a purine) in the area of neurotransmission and neurophysiology [1]. Along with basic purine neurophysiologic studies, the relevance of purinergic neurophysiologic mechanisms to human diseases was explored.

Receptors that bind to ATP are divided into two families: ionotropic receptors (P2X) and metabotropic receptors (P2Y). To date, seven P2X receptors (P2X1–P2X7) and eight P2Y receptors (P2Y1, 2, 4, 6, 11, 12, 13, and 14) have been recognized and characterized. Purinergic signaling, specifically in pain transduction, has been reviewed [2–4], as have therapeutic targets of purinergic signaling in the treatment of other diseases [5].

In urology, current available pharmacotherapeutic treatments for lower urinary tract symptoms (LUTS) focus on inhibition of adrenergic ($\alpha$1) and muscarinic (M2 and M3) pathways. The role of purinergic signaling in the regulation of urinary bladder function was established when published reports demonstrated that P2X2/P2X3 knockout animals had significantly altered bladder function [6, 7]. However, to date, no pharmacologic agent targeting the purinergic pathway has been developed for clinical use. Reviews of the role of ATP and purinergic signaling in the bladder and lower urinary tract function have been published [8–13].

The importance of the bladder urothelium to LUTS has only been investigated recently. Traditionally, the bladder urothelium and the constituent urothelial cells lining the bladder lumen are thought to act as a passive barrier. However, it is now accepted that the urothelial cells can act as "sensor-transducers," behaving like neurons in that they can respond to and release neurotransmitters [14, 15]. Not surprisingly then, P2X and P2Y receptors have been found to be expressed in urothelial cells and the urothelium [16, 17]. The importance of purinergic signaling to healthy umbrella urothelial cell function has been demonstrated [18].

Because purinergic signaling is important in both sensory transduction and bladder function, it is not

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surprising that purinergic signaling has been shown to be involved in various conditions, including interstitial cystitis/painful bladder syndrome (IC/PBS), spinal cord injury (SCI), bladder outlet obstruction (BOO), aging, and diabetes. Herein we review the literature related to recent investigations into purinergic signaling and bladder dysfunction, with a focus on translation to clinical conditions.

## Purinergic Signaling in Interstitial Cystitis/Painful Bladder Syndrome and Bladder Inflammation

IC/PBS is considered a chronic symptom complex made up of urinary frequency, urgency, nocturia, and bladder pain (the hallmark symptom). A pathophysiologic role of purinergic signaling has been proposed for IC/PBS [19, 20]. In one study, urinary ATP levels in patients with IC/PBS were found to be significantly higher than in controls, and the in vitro stretch of bladder urothelial cells from patients with IC/PBS released a significantly higher level of ATP than control cells [21]. Furthermore, in vitro stretch increased P2X3 expression in IC/PBS bladder urothelial cells more than in control bladder urothelial cells [22]. Other investigators have found similar changes in IC/PBS [17]. An animal model for IC/PBS, feline IC, has demonstrated similar changes in purinergic signaling in the bladder urothelium [23, 24]. These data suggest upregulation of purinergic signaling in the bladder urothelium as the etiology for the symptomatology seen in IC. Because P2X3/P2X2 are considered nociceptive receptors, an elevation in expression of this heteromeric receptor could mediate an increased sense of IC/PBS symptoms. Another possible contributor to IC/PBS symptoms is an augmented autocrine release of ATP by the bladder urothelium, even without stretch. It was shown that IC/PBS urothelial cells released significantly more ATP when exposed to varying concentrations of extracellular ATP [25].

Although it is not the perfect model of the IC/PBS condition, the cyclophosphamide-induced bladder injury model has been used to study bladder sensory transduction in response to chemically induced bladder inflammation. This model has shown significant alterations in purinergic signaling in bladder afferent pathways [26]. There was an increase in P2X receptor expression and/or function in both pelvic and lumbar splanchnic neural pathways, and this in turn contributed in part to the hypersensitivity associated with cystitis. The recently developed P2X3 and P2X2/P2X3 receptor antagonist A-317491 was studied in treatment of bladder overactivity caused by cyclophosphamide-induced cystitis [27]. The study found that A-317491 and another nonselective purinergic receptor antagonist, PPADS (pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonate), were effective in ameliorating the detrusor overactivity. Another study supported these findings [28].

Keay and colleagues [29] have published extensively on another possible causal factor in IC/PBS—that is, the production of a unique glycononapeptide, antiproliferative factor (APF), by IC/PBS bladder urothelial cells. A description of the link between APF and purinergic signaling in urothelial cells was published [30]. APF induced an augmented purinergic signaling in healthy bladder urothelial cells. Conversely, overcoming APF's action with heparin-binding epidermal growth factor-like growth factor (HB-EGF) (25) or the epidermal growth factor blocker genistein (30) in IC/PBS urothelial cells diminished the pathophysiologic augmented purinergic signaling.

In summary, a body of literature has demonstrated altered (upregulated) purinergic signaling in IC/PBS urothelium/urothelial cells. Whether this is a primary or secondary effect is not known at this time. Nevertheless, potential future therapies for IC/PBS and possibly other noninfectious inflammatory bladder conditions include blocking urothelial and/or neural purinergic signaling.

## Purinergic Signaling in Voiding Dysfunction Caused by Spinal Cord Injury

Several review articles have summarized the role of purinergic signaling in bladder functional changes induced by SCI [31, 32]. A clinical study compared bladder immunohistochemical staining of purinergic receptors in 15 patients with bladder dysfunction secondary to SCI and in 11 patients with bladder disorders not related to SCI [33]. This study found that a tendency toward stronger P2X2 staining in specimens from patients with spinal cord lesions. A selective P2X2/P2X3 purinergic receptor antagonist (A-317491) has been investigated in treatment of detrusor overactivity induced by SCI in an animal model [34]. This antagonist, given intravenously, showed the ability to reverse detrusor overactivity by increasing voiding interval, reducing nonvoiding contractions, and increasing pressure threshold for voiding. However, the amplitude of the voiding contractions was unchanged by this antagonist. The authors theorized that this antagonist was acting on the P2X2/P2X3 receptors on the bladder afferent nerves. From the efferent motor side, a study of rabbit bladder after SCI found that neurally mediated bladder contractility (with electrical field stimulation [EFS]) shifted from purinergic predominance to cholinergic predominance [35]. Adding to this complexity, investigators have studied ATP release from the spinal cord of rats with SCI in response to urothelial mechanosensory cholinergic receptor activation. These investigators found significantly higher spinal ATP release in SCI compared with non-SCI rats [36].

Within the spinal cord, neuronal purinergic regulation also plays an important role in SCI. There was excessive release of ATP by the traumatized spinal tissue followed by activation of P2X7 receptors [37]. P2X7 receptor inhibition can improve recovery after SCI. The P2X7 receptor antagonists oxidized ATP and PPADS significantly improved functional recovery and diminished cell death in the peritraumatic zone. SCI was also associated with prolonged purinergic receptor activation, which results in excitotoxicity-based neuronal degeneration.

Brilliant blue G, another P2X7 receptor antagonist, directly reduced local activation of astrocytes and microglia, as well as neutrophil infiltration after SCI [38•]. These observations suggested that brilliant blue G not only protected spinal cord neurons from purinergic excitotoxicity but also reduced local inflammatory responses. All these therapeutic studies may lead to another new avenue, based on modulation of purinergic signaling as future treatment of SCI [39], which ultimately may prevent SCI-related bladder dysfunction.

Studies of purinergic signaling plasticity in spinal cord development may be important in future treatment of SCI aimed at repairing the injury site. Expression of P2X2 and P2X3 receptors in the bladder and spinal cord of postnatal and adult rats demonstrated plasticity of expression of P2X2 and P2X3 receptors in the bladder and spinal cord during early postnatal development, at times coincident with the appearance of mature voiding patterns [40]. Purinergic signaling is important in the regulation of neural myelination and plays a role in plasticity and neural development in general [41].

Therefore, the role of purinergic signaling related to SCI is complex. Purinergic signaling affects bladder function at both the central and peripheral nervous system levels. Furthermore, at the peripheral level, purinergic signaling affects both the afferent and efferent components regulating bladder function. Purinergic signaling also has a role in neural development, plasticity, and repair. Finally, purinergic signaling can be altered at the detrusor smooth muscle and bladder urothelial level.

Urologists recently have become interested in the use of botulinum toxin A (BTX-A) to treat neurogenic detrusor overactivity. BTX-A had been reported to markedly reduce ATP release in SCI rat bladders [42]. BTX-A is internalized by presynaptic neurons after binding to an extracellular receptor (ganglioside and presumably synaptic vesicle protein 2C). It is believed that BTX-A disrupts fusion of the acetylcholine-containing vesicle within the neuronal wall by cleaving the synaptosomal-associated protein-25 in the synaptic fusion complex in the neuronal cytosol; therefore, the net effect of BTX-A treatment is selective paralysis of the low-grade contractions of the unstable detrusor while still allowing high-grade contraction that initiates micturition. Additionally, BTX-A seems to have effects on afferent nerve activity by modulating the release of ATP in the urothelium; blocking the release of substance P, calcitonin gene-related peptide, and glutamate from afferent nerves; and reducing levels of nerve growth factor. These effects on sensory feedback loops might not only help explain the mechanism of BTX-A in relieving symptoms of overactive bladder (OAB) but also suggest a potential role for BTX-A in the relief of hyperalgesia associated with lower urinary tract disorders [43, 44].

## Purinergic Signaling in Voiding Dysfunction Caused by Bladder Outlet Obstruction and Overactive Bladder

Purinergic signaling may have a role in voiding dysfunction caused by BOO. Human detrusor muscle from BOO patients exhibited atropine-resistant contractions abolished by the ATP competitive analogue α,β-methylene-ATP, suggesting that these contractions were mediated by neurally released ATP [45]. A similar result was found when investigators studied BOO in a rabbit model. Investigators found that in response to EFS, which causes release of neurotransmitters from postsynaptic motor nerves, the purinergic component of nerve-mediated detrusor contraction was increased in the early stages of BOO in rabbits [46]. Furthermore, the purinergic component mediating BOO detrusor contractions was predominant compared with the cholinergic (muscarinic) component. Another study suggested that blocking the purinergic component may be helpful in addition to antimuscarinics in blocking BOO-induced detrusor overactivity [47]. However, this concept was challenged by other investigators who showed no change in purinergic signaling within the rat bladder after BOO [48]. There were no measurably different physiologic responses of the rat obstructed bladder to purinergic agonists or qualitative changes observed in the immunohistology for P2X receptor subtypes. Similarly, another study of rat BOO found no change in P2X1 receptor immunoactivity in smooth muscle between the BOO rat and a control rat [49], although there was attenuated contractile response of the BOO bladders in response to ATP. P2X1 mRNA was also not found to be different in obstructed and nonobstructed human bladders [50].

The role of purinergic signaling in the urothelium from BOO bladders also has been studied. There was evidence of increased P2X3 expression in the urothelium of the BOO group [51]. In vitro stretch of the bladder urothelial cells from benign prostatic hyperplasia (BPH) patients released significantly more ATP than did the urothelial cells from control patients [52]. This study also showed that doxazosin, an α1-adrenoceptor blocker, blocked this purinergic

mechanism, suggesting that the mechanism of action of α1-blocker use in BPH may involve a urothelial purinergic pathway.

Purinergic antagonists also have been evaluated in the treatment of BOO in animal models. A study using one of the nonselective purinergic antagonists (suramin) and the α1-adrenergic antagonists terazosin and BMY 7378 on conscious rats with BOO found that purinergic signaling was involved in α1-adrenergic receptors' effect on the bladder instability induced by BOO [53].

Investigators measured whether the improvement of LUTS was correlated with urinary ATP levels [54]. This group recruited 57 patients and 13 healthy controls. All the male patients had BPH, and all female patients had OAB. They examined LUTS and urinary ATP/creatinine ratio before and after treatment. The study found that in BPH patients, administration of tamsulosin decreased LUTS and the urinary ATP/creatinine ratio. In the OAB patients, administration of propiverine hydrochloride decreased LUTS and urinary ATP/creatinine ratio. The study also found that improvement of LUTS was greater in patients with a higher baseline urinary ATP level. It was suggested that urinary ATP could become a marker of LUTS.

## Purinergic Signaling in Voiding Dysfunction Caused by Aged Bladder

Age-related changes in the structure and function of the bladder may contribute to the high prevalence of voiding dysfunction in the older adult population. Physiologic and neurochemical studies have been conducted in human detrusor strips obtained from different aged individuals, focusing on potential changes in cholinergic and purinergic neurotransmission [55]. These investigators found a significant positive association between age and purinergic neurotransmission and a significant negative correlation between age and cholinergic neurotransmission in human isolated bladder smooth muscle [56]. Other physiologic and microdialysis experiments indicated that purinergic transmission increases, whereas cholinergic transmission decreases with age. These effects are most likely a result of decreased release of acetylcholine and increased release of ATP from postganglionic parasympathetic axons innervating the bladder. This increased ATP release resulting from aging was theorized to cause decreased—or down-regulation of—P2X1 mRNA expression in aged human bladder smooth muscle [50].

The effects of purinergic signaling pathways also had been studied in aged bladders. A study found a correlation between increases in post-washout contractions (after washing out ATP) and changes in sensory and voiding mechanisms in aged rat urinary bladders [57]. The investigators suggested that the ATP-induced post-washout contraction in rats was not directly mediated by P2X purinergic receptors but instead resulted from the synthesis of prostaglandins, especially $E_2$, which is a sensory autacoid.

## Purinergic Signaling in Voiding Dysfunction Caused by Diabetes

The cholinergic-mediated, purinergic-mediated, and peptidergic (capsaicin-sensitive, tachykinin-mediated) contractions were evaluated in streptozotocin-induced diabetic rats by several groups. One group had found that detrusor smooth muscle from diabetic rats had a higher response to EFS than that of the control group [58]. This group also found that contractions to EFS in the presence of PPADS and suramin were reduced by 66% by atropine but were left unchanged by capsaicin or diabetes. This study concluded that experimental diabetes selectively impairs peptidergic, capsaicin-sensitive responses (especially those that involve impulse conduction) in the rat detrusor smooth muscle. The study also presumed that the EFS contractile response remaining after muscarinic and purinergic blockade was mediated by a yet-unknown neurotransmitter. Another group compared the proportions of cholinergic, purinergic, and residual nonadrenergic-noncholinergic components of contractile responses among the three groups of animals: streptozotocin-induced diabetes, 5% sucrose–induced diuresis, and age-matched controls [59]. These investigators found that diabetes caused a significant reduction in body weight compared with diuresis and controls, although the bladders of diabetic and diuretic rats weighed more than those of the controls. Both diabetes and diuresis caused a significant increase in fluid intake, urine output, and bladder size. Diabetes and diuresis caused similarly increased response to EFS and reduced response to the cholinergic component compared with controls. However, the purinergic response was significantly smaller in diuretic bladder strips compared with controls, but not in diabetic rats. A residual nonadrenergic-noncholinergic component of unknown origin increased significantly but differently in diabetics and diuretics compared with controls. A similar study using diabetes mellitus–associated rabbits showed a significant decrease in the cholinergic nerve-mediated component and a significant increase in the purinergic nerve-mediated component compared with controls [60]. These results suggest that an enhancement of purinergic and a reduction in cholinergic neurotransmission occur in the detrusor muscle of the diabetic rabbit. These changes may contribute to the pathophysiology of diabetic cystopathy.

In a study that aimed to investigate whether diabetes altered the expression of the gap junction protein con-

nexin43 (Cx43), investigators described concomitant alterations in purinergic signaling in the urinary bladder [61]. A significant positive correlation between bladder spontaneous activity and P2Y4 receptor expression levels was found. The investigators noted that changes in Cx43 and P2 receptor expression were largely prevented by insulin therapy. These detailed studies yielded the conclusion that diabetes mellitus markedly altered the expression of the gap junction protein Cx43 and of P2Y4 receptor subtype in the urinary bladder.

## Conclusions

Alterations in purinergic signaling have been described in bladder dysfunction secondary to IC/PBS, neurogenic detrusor from SCI, chemical cystitis, OAB/LUTS, diabetes, and aging. The tissue sites of purinergic signaling include the spinal cord, peripheral nerves (sensory and motor), detrusor smooth muscle, and bladder urothelium. Although this diversity of sites points to the importance of purinergic signaling in the control of bladder function, targeting a specific site may be difficult. As more research is conducted, our understanding of how to harness the purinergic system in promoting urinary storage and/or emptying may be realized.

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