Which of the primary prostaglandin receptors might play a role in lower urinary tract dysfunction? A narrative review

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ABSTRACT

This article reviews the role of inflammation in bladder dysfunction, and the potential for prostaglandins to play a contributing role. If this is the case, it presents this receptor system as a future therapeutic target, and also enhances our knowledge into the mechanisms underlying lower urinary tract function.

Keywords: urinary bladder; inflammatory mediators; prostaglandins; prostanoids; histamine.

Urinary bladder inflammation has been observed in various lower urinary tract disorders, including interstitial cystitis/bladder pain syndrome (IC/BPS)¹ and overactive bladder (OAB)². There are currently limited pharmaceutical options to selectively target the inflammation present in either IC/BPS or OAB. Antimuscarinic medicines, which act on the activity of smooth muscle, have been used as the first-line pharmacological treatment for OAB. For IC/BPS, treatments such as dimethylsulfoxide (DMSO), a bladder instillation that can assist in reducing inflammation and pain, as well as pentosan polysulphate, an oral medicine which works to protect the bladder epithelium, do not act on the associated bladder inflammatory mechanisms. This presents opportunities for future research to identify novel therapeutic approaches for the treatment of IC/BPS and OAB, with the target of inhibiting bladder inflammation. As such, recent advances in the research surrounding our understanding of the role of inflammatory mediators in bladder dysfunction warrant a review.

It is reported that there is an increase in the presence of inflammatory mediators within the bladder wall³ and urine⁴ of patients diagnosed with OAB or IC/BPS. The mediators include histamine⁵, nerve growth factor, serotonin/5-HT^{6,7}, proteases, chemokines and prostaglandins released either from nearby mast cells, or synthesised within the cells lining the bladder wall⁸. These reports often correlate to clinical findings, such

as where significantly increased expression of histamine receptors have been noted in people presenting with BPS/IC⁹. The actions of many inflammatory mediators can induce immediate urinary bladder contractions^{7,10-12} and sensitise afferent nerve endings to result in an increased spinal cord neuronal activation¹³. This is of importance, as inflammatory mediators operate upon pathophysiological mechanisms which are not targeted by current approved therapies for IC/BPS nor OAB. There is also increasing evidence that the actions of inflammatory mediators are altered in ageing^{14,15}. Therefore, inflammation and the actions of these pro-inflammatory mediators may contribute to the development of the urinary frequency and urgency symptoms observed in OAB, and pain in IC/BPS.

All prostaglandins are synthesised from arachidonic acid, which is a polyunsaturated omega-6 fatty acid released from cell membranes via the hydrolysis of the SN-2 bond by the phospholipase A2 enzyme¹⁶. Two cyclooxygenase isoforms, COX-1 and COX-2, metabolise arachidonic acid into prostaglandin H2 which is subsequently converted into five primary prostaglandins via their respective synthases: prostaglandin E2, prostaglandin D2, prostaglandin F2 α , prostaglandin I2 (also called prostacyclin) and thromboxane. These inflammatory mediators exert their functions through the stimulation of eight specific guanine nucleotide-binding proteins (G-protein) coupled receptors: prostaglandin E2 receptor 1-4 (EP1-4), prostaglandin D2 receptor (DP), prostaglandin

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F receptor (FP), prostaglandin I₂ receptor (IP) and thromboxane receptor (TP), respectively¹⁷. G-protein-coupled receptors are cell membrane proteins that convert extracellular signals into intracellular responses. These signals include responses to neurotransmitters, hormones and chemical mediators like prostaglandins. Of the five prostaglandins produced endogenously within the bladder wall, prostaglandin E₂ is thought to be the most likely contributor to bladder dysfunction. It is involved in the control of normal continence via afferent signalling and the involvement in detrusor overactivity has been proposed by its ability to sensitise capsaicin-sensitive afferent nerve endings¹⁸.

Generally, the stimulation of EP₁ and EP₃ receptors are thought to cause bladder contractions, whereas EP₂ and EP₄ induce bladder relaxation¹⁹. Indeed, the EP₁ receptor is involved in initiating micturition in both humans and animals, and has been shown to be responsible for OAB in models of bladder obstruction²⁰. In the isolated guinea pig bladder, application of prostaglandin E₂ resulted in increased amplitude of urinary bladder phasic contractions without affecting the frequency of these contractions²¹. In studies involving pig tissue, treatment with prostaglandin E₂ induced significantly enhanced tonic contractions and increased the frequency of phasic contractions in both urothelium with lamina propria (U&LP) and detrusor smooth muscle tissue strips²², presenting as a potentially significant contributor to contractile activity. The stretch-induced release of prostaglandin E₂ from the urothelium has been suggested to exert a direct effect upon detrusor smooth muscle cells to evoke contractions or to enhance the release of local adenosine triphosphate (ATP) via stimulation of EP₁ receptors, resulting in an increased afferent nerve activation²³ and subsequent signalling. As ATP is involved in signalling the sensation of bladder fullness to the central nervous system²⁴, increased neuronal activation could thus trigger the micturition reflex and feelings of urgency, and this provides an interesting avenue for future research.

The role of other prostaglandins in the urinary bladder has also been explored in the literature, albeit to a lesser extent. The major prostaglandin released from mast cells at sites of inflammation is prostaglandin D₂, which has been shown to inhibit nerve stimulation-induced detrusor smooth muscle contractions in strips of guinea pig bladder²⁵. The prostacyclin antagonists decrease neurogenic detrusor overactivity in spinal cord-injured rats²⁶ by significantly enhancing the interval between voiding and voiding volume. Similarly, a decrease in the frequency of bladder contractions and increased micturition threshold was observed in citric acid induced detrusor overactivity²⁷ in the presence of prostacyclin antagonist. Thromboxane and prostaglandin F₂ α have been shown to induce direct contractions of the isolated human detrusor²⁸ and U&LP²⁹. However, there remains a great paucity of research into the impacts of prostaglandin agonists on human tissues, demonstrating a clear need for future studies in this area.

U&LP strips taken from the two most superficial layers of the bladder lumen are known to exhibit spontaneous phasic contractions in the absence of any stimulation³⁰. These spontaneous contractions are thought to be propagated by the muscularis mucosae present within the U&LP³¹ and are capable of modulating the overall bladder function. Immunohistochemical analysis has demonstrated that this muscularis mucosae layer is distinct from its adjacent detrusor smooth muscle layers and has been observed in pig, human and guinea pig bladders³¹. This is further reinforced with the observation that U&LP preparations continue to develop large spontaneous contractions after the apical urothelial layer and larger blood vessels are removed³². Nonetheless, these spontaneous contractions occurring in rat U&LP arise from noradrenaline stimulation of the vasculature³³ which remains similar to that observed in pig tissue³⁴. The impact of prostaglandin agonists on U&LP contractility and influence to increase the frequency of spontaneous phasic contractions and decrease the amplitude is of interest, due to growing evidence for this system's role in modulating detrusor smooth muscle contractions³⁵. Identifying receptor systems capable of modulating bladder activity presents the possibility for developing novel therapeutic approaches for inhibiting inflammatory mediator-induced contractile responses.

Of particular interest is histamine, which has been shown to increase the frequency of phasic contractions and decrease their amplitude in porcine U&LP while initiating these phasic contractions in the detrusor^{5,14}. The increases in tonic contractions and phasic activity observed in response to histamine are comparable to those observed after treatment with prostaglandin E₂. Rahnema'i et al.²¹ reported that treatment with prostaglandin E₂ reduced the amplitudes of phasic contractions in intact guinea pig bladders. However, the link to humans has never been investigated, presenting an interesting avenue for research into the potential of the histamine and prostaglandin receptor systems to underlie some presentations of bladder dysfunctions such as OAB and IC/BPS.

From the current literature, the prostaglandin system, with a particular interest in EP₁ to EP₄ receptors, could be a novel target for pharmaceutical treatments and should be explored further. The mechanism of action for these prostaglandin responses may present an additional therapeutic target in the treatment of OAB or IC/bladder pain syndrome.

REFERENCES

1. Grover S, Srivastava A, Lee R, et al. Role of inflammation in bladder function and interstitial cystitis. *Ther Adv Urol* 2011;3(1):19–33.
2. Comperat E, Reitz A, Delcourt A, et al. Histologic features in the urinary bladder wall affected from neurogenic overactivity: a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. *Eur Urol* 2006;50(5):1058–64.

3. Kastrup J, Hald T, Larsen S, et al. Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. *Br J Urol* 1983;55(5):495-500.
4. Furuta A, Yamamoto T, Suzuki Y, et al. Comparison of inflammatory urine markers in patients with interstitial cystitis and overactive bladder. *Int Urogynecol J* 2018;29(7):961-6.
5. Stromberga Z, Chess-Williams R, Moro C. Histamine modulation of urinary bladder urothelium, lamina propria and detrusor contractile activity via H1 and H2 receptors. *Sci Rep* 2019;9(1):3899.
6. Matsumoto-Miyai K, Yamada E, Shinzawa E, et al. Serotonergic regulation of distention-induced ATP release from the urothelium. *Am J Physiol Renal Physiol* 2016;310(7):F646-f55.
7. Moro C, Edwards L, Chess-Williams R. 5-HT2A receptor enhancement of contractile activity of the porcine urothelium and lamina propria. *Int J Urol* 2016;23(11):946-51.
8. Rahnama'i MS, Van Koeveeringe GA, Van Kerrebroeck PE. Overactive bladder syndrome and the potential role of prostaglandins and phosphodiesterases: an introduction. *Nephrourol Mon* 2013;5(4):934-45.
9. Shan H, Zhang E-W, Zhang P, et al. Differential expression of histamine receptors in the bladder wall tissues of patients with bladder pain syndrome/interstitial cystitis – significance in the responsiveness to antihistamine treatment and disease symptoms. *BMC Urol* 2019;19(1):115.
10. Štromberga Z, Chess-Williams R, Moro C. The role of histamine in modulating urothelial contractile activity. *ANZ Continence J* 2017;23(4).
11. Moro C, Chess-Williams R. Non-adrenergic, non-cholinergic, non-purinerger contractions of the urothelium/lamina propria of the pig bladder. *Auton Autacoid Pharmacol* 2012;32(3 Pt 4):53-9.
12. Moro C, Leeds C, Chess-Williams R. Contractile activity of the bladder urothelium/lamina propria and its regulation by nitric oxide. *Eur J Pharmacol* 2012;674(2-3):445-9.
13. Davidson S, Copits BA, Zhang J, et al. Human sensory neurons: membrane properties and sensitization by inflammatory mediators. *Pain* 2014;155(9):1861-70.
14. Stromberga Z, Chess-Williams R, Moro C. Alterations in histamine responses between juvenile and adult urinary bladder urothelium, lamina propria and detrusor tissues. *Sci Rep* 2020;10(1):4116.
15. Moro C, Stromberga Z, Chess-Williams R. The effects of age on contractile activity of the bladder urothelium and detrusor. *ANZ Continence J* 2018;24(3).
16. Clark JD, Lin LL, Kriz RW, et al. A novel arachidonic acid-selective cytosolic PLA2 contains a Ca(2+)-dependent translocation domain with homology to PKC and GAP. *Cell* 1991;65(6):1043-51.
17. Woodward DF, Jones RL, Narumiya S. International Union of Basic and Clinical Pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress. *Pharmacol Rev* 2011;63(3):471-538.
18. Maggi CA. Prostanoids modulate reflex micturition by acting through capsaicin-sensitive afferents. *Eur J Pharmacol* 1988;145:105-12.
19. Coleman RA, Smith WL, Narumiya S. International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. *Pharmacol Rev* 1994;46:205-29.
20. Lee T, Hedlund P, Newgreen D, et al. Urodynamic effects of a novel EP1 receptor antagonist in normal rats and rats with bladder outlet obstruction. *J Urol* 2007;177:1562-7.
21. Rahnama'i MS, van Koeveeringe GA, van Kerrebroeck PEV, et al. The effect of indomethacin on the muscarinic induced contractions in the isolated normal guinea pig urinary bladder. *BMC Urol* 2013;13(1):8.
22. Stromberga Z, Chess-Williams R, Moro C. Prostaglandin E2 and F2alpha modulate urinary bladder urothelium, lamina propria and detrusor xontractility via the FP receptor. *Front Physiol* 2020;11(705).
23. Wang X, Momota Y, Yanase H, et al. Urothelium EP1 receptor facilitates the micturition reflex in mice. *Biomed Res* 2008;29(2):105-11.
24. Cheng Y, Mansfield KJ, Allen W, et al. ATP during early bladder stretch is important for urgency in detrusor overactivity patients. *Biomed Res Int* 2014;2014:204604.
25. Guan NN, Svennersten K, de Verdier PJ, et al. Receptors involved in the modulation of guinea pig urinary bladder motility by prostaglandin D2. *Br J Pharmacol* 2015;172(16):4024-37.
26. Khera M, Boone TB, Salas N, et al. The role of the prostacyclin receptor antagonist RO3244019 in treating neurogenic detrusor overactivity after spinal cord injury in rats. *BJU Int* 2007;99:442-6.
27. Cefalu JS, Zhu QM, Eggers AC, et al. Effects of the selective prostacyclin receptor antagonist RO3244019 on the micturition reflex in rats. *J Urol* 2007;178(6):2683-8.
28. Palea S. Pharmacological characterization of thromboxane and prostanoid receptors in human isolated urinary bladder. *Br J Pharmacol* 1998;124:865-72.
29. Stromberga Z, Chess-Williams R, Moro C. The five primary prostaglandins stimulate contractions and phasic activity of the urinary bladder urothelium, lamina propria and detrusor. *BMC Urol* 2020;20(1):48.
30. Moro C, Uchiyama J, Chess-Williams R. Urothelial/ lamina propria spontaneous activity and the role of M3 muscarinic receptors in mediating rate responses to stretch and carbachol. *Urology* 2011;78(6):1442.e9-15.
31. Mitsui R, Lee K, Uchiyama A, et al. Contractile elements and their sympathetic regulations in the pig urinary bladder: a species and regional comparative study. *Cell Tissue Res* 2019;379(2):373-87.
32. Lee K, Mitsui R, Kajioka S, et al. Role of PTHrP and sensory nerve peptides in regulating contractility of muscularis mucosae and detrusor smooth muscle in the guinea pig bladder. *J Urol* 2016;196(4):1287-94.
33. Shimizu Y, Mochizuki S, Mitsui R, et al. Neurohumoral regulation of spontaneous constrictions in suburothelial venules of the rat urinary bladder. *Vascul Pharmacol* 2014;60(2):84-94.
34. Moro C, Tajouri L, Chess-Williams R. Adrenoceptor function and expression in bladder urothelium and lamina propria. *Urology* 2013;81(1):211.e1-7.
35. Chakrabarty B, Bijos DA, Vahabi B, et al. Modulation of bladder wall micromotions alters intravesical pressure activity in the isolated bladder. *Front Physiol* 2019;9(1937).