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

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Published in:
Australian and New Zealand Continence Journal

Published: 01/09/2020

Document Version:
Publisher's PDF, also known as Version of record

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For referencing Stromberga Z & Moro C. Which of the primary prostaglandin receptors might play a role in lower urinary tract dysfunction? A narrative review. Australian and New Zealand Continence Journal 2020; 26(3):58-60

DOI https://doi.org/10.33235/anzcj.26.3.58-60

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 wall[3] and urine[4] of patients diagnosed with OAB or IC/BPS. The mediators include histamine[5], 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 wall[8]. These reports often correlate to clinical findings, such as where significantly increased expression of histamine receptors have been noted in people presenting with BPS/IC[9]. 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 activation[13]. 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 enzyme[16]. 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 F2α, 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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Competing interest statement
The authors have declared they have no relevant relationships or circumstances that present an actual or potential conflict of interest.

F receptor (FP), prostaglandin I2 receptor (IP) and thromboxane receptor (TP), respectively[17]. 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 endings[18].

Generally, the stimulation of EP1 and EP3 receptors are thought to cause bladder contractions, whereas EP2 and EP4 induce bladder relaxation[19]. 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 obstruction[20]. 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 contractions[21]. 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 strips[22], 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 activation[23] and subsequent signalling. As ATP is involved in signalling the sensation of bladder fullness to the central nervous system[24], 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 bladder[25]. The prostacyclin antagonists decrease neurogenic detrusor overactivity in spinal cord-injured rats[26] 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 overactivity[27] in the presence of prostacyclin antagonist. Thromboxane and prostaglandin F2α have been shown to induce direct contractions of the isolated human detrusor[28] and U&LP[29]. 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 stimulation[30]. These spontaneous contractions are thought to be propagated by the muscularis mucosae present within the U&LP[31] 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 bladders[31]. 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 removed[32]. Nonetheless, these spontaneous contractions occurring in rat U&LP arise from noradrenaline stimulation of the vasculature[33] which remains similar to that observed in pig tissue[34]. 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 contractions[35]. 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. Rahnama'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.

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