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New insights into the pharmacology of the bladder

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Abstract

Purpose of review—Pharmacotherapy of a number of bladder disorders has traditionally focused on targeting the 'sensory' component or bladder nerves and the smooth muscle. This review aims to provide an insight into recent (experimental and clinical) developments in mechanisms of existing therapies as well as novel targets.

Recent findings—Traditionally, sensory signaling in the urinary bladder has been attributed to activation of bladder afferents, but new findings have pointed to the urothelium and interstitial cells as key participants in the transduction of sensory events. Recent advances provide strong support for the development of subtype selective receptor agonists/antagonists, the modulation of signal transduction cascades and new and expanded uses for various neurotoxins.

Summary—The development of therapeutic options for the treatment of a number of bladder disorders is complicated, and most treatments are associated with an increased incidence of side effects or lack of specificity. Recent studies suggest that selective targeting of receptors/ion channels or a disease-specific (i.e. phosphorylated) form of the receptor may represent a viable therapeutic target. Though the mechanisms regulating ion channel expression under pathological conditions are not fully known, an increased understanding of these pathways has important implications for drug development.

Keywords

botulinum toxin; phosphodiesterase inhibitors; purines; Rho kinase; transient receptor potential channels; urothelium

Introduction

While the etiologies of many urinary bladder voiding or storage disorders are not fully understood, it seems likely that alterations in connectivity/excitability of key elements of a peripheral 'sensory web' including sensory afferents, smooth muscle, the urothelium and interstitial cells could lead to disorders of the urogenital tract. This review highlights key pharmacologic therapy areas, including targeting of specific receptors/ion channels, modulation of signal transduction pathways as well as use of neurotoxins, with regard to the clinical management of bladder disorders.

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Transient receptor potential channels

Currently, 28 transient receptor potential (TRP) channels are known and a number of these associated with osmo-regulation, thermal, chemical and mechanical signaling mechanisms are expressed within the lower urinary tract [1]. TRPV1 is by far the best characterized and has been identified in bladder afferents as well as smooth muscle, urothelial cells and those cells termed 'myofibroblasts' or 'interstitial' cells, though the biological role of many of these channels in urinary bladder function still remains elusive [2,3]. Charrua *et al*. [4] has studied bladder function in TRPV1-null mice following chemical-induced cystitis and suggested a role for TRPV1 in inflammatory conditions. Further, there is also the possibility that changes in regional TRP bladder expression may be linked to function, as Liu *et al*. [5•] have found that symptoms of sensory urgency are associated with increased TRPV1 expression in the trigonal mucosa.

Intravesical vanilloids (capsaicin; resiniferatoxin) have been beneficial in treating a number of bladder disorders including neurogenic bladder or hypersensitivity disorders such as interstitial cystitis. While intravesical therapy has largely been abandoned due to discomfort and poor bioavailability, there may be renewed support in the utilization of resiniferatoxin in treatment of interstitial cystitis [2], as well as in overactive bladder (OAB) patients with refractory urgency [6] and in benign prostatic hyperplasia (BPH) with OAB symptoms [7]. Resiniferatoxin has recently been shown to alter nonneural (spontaneous or autonomous) bladder contractions and this may be due to an effect on local TRPV1 targets [8••]. It is hypothesized that this action may play a role in the treatment of detrusor overactivity. In support is evidence of a correlation between successful intravesical resiniferatoxin treatment in patients with idiopathic detrusor overactivity (refractory to antimuscarinics) and increased mucosal/submucosal TRPV1 expression [9•].

There is emerging evidence that TRPV1 may also play an important role in 'normal' voiding function. Daly *et al*. [10••] recorded bladder afferents in TRPV1 null mice and found a decreased response in low threshold bladder fibers to bladder filling. Additional studies [11,12], together with previous reports that TRPV1 is essential for mechanically evoked purinergic signaling by the urothelium [13], provide functional significance that TRPV1 in the bladder extends beyond an involvement in pain sensation to include participation in normal voiding functions.

Two other TRPs may also have a role in bladder function. There is evidence that TRPV4, a channel which can be activated by hypo-osmolarity, heat or certain lipid compounds, and seems to be expressed mainly by urothelial cells, may play a role in bladder function. While in mice deletion of this channel results in impaired voiding responses [14••], intravesical instillation of a TRPV4 agonist in the rat triggers a novel voiding reflex which could regulate the late phase of contraction [15••]. In the awake ewe, TRPV4 may also be involved in a urethra to bladder reflex, proposed to facilitate bladder emptying [16]. Another member of the TRP family, TRPA1, is expressed in C-fiber afferents as well as urothelium and agonists to this channel induce bladder hyperreflexia [17••,18]. Of interest is the finding that hydrogen sulfide, which may be formed during infection/inflammation, is an activator of TRPA1 [17••]. While the significance of these TRPs in the normal and pathological bladder is not yet known, it is interesting to speculate that both could be potential targets for bladder urgency.

ATP and purinergic receptors

Since the first report (1997) of distension-evoked ATP release from the urinary bladder, a large amount of evidence supports a role for urothelial-derived ATP release in both autocrine and paracrine signaling [19,20••]. In addition, by activation of a population of

suburothelial bladder nerves, urothelial-derived ATP release during distension could trigger sensations of fullness and pain or induce changes in bladder activity [21•]. Both P2X receptor agonists as well as inflammation have been shown to increase bladder afferent firing [22]. Recently, Kumar *et al*. [23••] reported a significant increase in ATP release from the urothelium of patients with painful bladder syndromes, suggesting that this type of noncholinergic mechanism may play a role in bladder pathology.

P2X and P2Y receptors are expressed in various types of cells located at or near the luminal surface of the urinary bladder, suggesting that ATP has an important role in chemical communication [24]. Chopra *et al*. [25••] showed the existence of functional urothelial P2Y2/P2Y4 receptors and activation of these receptors could have a role in autocrine/paracrine signaling throughout the urothelium. In addition, Fry *et al*. [26••] have recently described functional P2Y6 receptor expression within the suburothelial myofibroblasts, which may play an important role in integrating or amplifying the response to bladder distension. Alterations in receptor sensitivity and expression suggest a role for ATP signaling in disease. In rats with bladder outlet obstruction (BOO), Kim *et al*. [27] reported a significant increase in P2X3 receptor expression within the mucosa but not smooth muscle. While Chua *et al*. [28•] reported no change in P2X1 receptor expression in the obstructed detrusor, these authors did find a significant decrease in P2X1 receptor expression with age in the male detrusor. This may be due to increased release of ATP in the aging bladder. Kennedy *et al*. [29••] have described a component of the neurogenic contraction (resistant to both atropine and P2X1 antagonism), which could be a novel therapeutic target for bladder disorders.

Phosphodiesterase inhibitors

Phosphodiesterase isoenzymes function by regulating the levels of second messengers (cAMP/cGMP), which affect biological processes including smooth muscle tone in urogenital tissues [30•]. There is evidence that these agents may be helpful in treatment of lower urinary tract symptoms (LUTSs) including BPH, due to relaxation effects of bladder, urethral and prostatic smooth muscle. The use of selective inhibitors of phosphodiesterase isoenzymes affords a degree of organ selectivity, as both distribution and function vary according to tissue. For example, while phosphodiesterase isoenzymes 1 and 4 (PDE1 and PDE4) may affect (detrusor) smooth muscle, PDE5 is thought to act mainly in the vasculature and urethra and inhibition may improve symptoms of BPH-associated LUTSs [30•,31].

Though the mechanism by which PDE5 inhibitors (PDE5i) improve LUTSs is not known, it has been hypothesized that it may involve relaxation effects on urethral smooth muscle or structures involved in afferent signaling [30•]. Yanai *et al*. [32••] postulated that the PDE5i (sildenafil) acts by suppressing smooth muscle (multibundle) spontaneous activity. In rats with BOO, treatment with the PDE5i vardenafil significantly reduced nonvoiding contractions [33], while in a rat model for BPH, Kang *et al*. [34] found that the selective PDE5 inhibitor, DA8159, decreased urethral pressures. Randomized studies using the PDE5 inhibitor sildenafil alone or in combination with the α-1 blocker alfuzocin report significant improvements in LUTSs [35–37]. A recent double-blind trial (twice daily treatment with vardenafil) showed significant improvement in irritative and obstructive LUTSs as well as quality of life in men with BPH/LUTSs [38]. In BOO rats, a selective PDE4 inhibitor (IC485) administered alone or in combination with the antimuscarinic tolteradine was found to reduce detrusor overactivity [39]. Oger *et al*. [40••] showed that the PDE4 inhibitor, rolipram, decreased amplitude/frequency of human smooth muscle contractility. Taken together, these studies point to a role for modulation of phosphodiesterase isoenzymes in the future treatment of patients with lower urinary tract dysfunctions such as OAB.

Beta-3 adrenergic agonists

Patients with OAB are typically treated with muscarinic receptor antagonists. Increased incidence of side effects as well as poor efficacy in some patients, however, has sparked interest in the development of new β-adrenoceptor subtype-specific agonists, as therapeutic agents. β_3-adrenoceptor is reported to be the predominant receptor subtype expressed in human bladder [41] making it an attractive target, with less incidence of cardiovascular and pulmonary side effects, due to activation of β2-adrenoceptor [42••]. Clouse *et al*. [43] and Badawi *et al*. [44] reported that β_3-adrenoceptor activation plays a major role in detrusor muscle relaxation in studies (*in vitro*) using rat and human bladder strips, respectively. A number of β_3-adrenoceptor specific agonists are currently being evaluated as potential treatment for OAB in humans and are at both preclinical and early clinical development stages; these include GW427353 (GlaxoSmithKline, Brentford, UK) and YM178 (Astellas, Tokyo, Japan) [45].

Biers *et al*. [46] reported that GW427353 produced significant relaxation of bladder smooth muscle tone, at low concentrations, with in-vitro studies using urothelium-denuded bladder strips from 'normal' human donors. Hicks *et al*. [47] studied the effects of GW427353 in the anesthetized dog and found that the agonist evoked an increase in bladder capacity under conditions of acid-evoked bladder hyperactivity, without affecting voiding efficiency.

Takaku *et al*. [48] reported that the specific β_3-adrenoceptor agonist, YM187, mediated muscle relaxation in human bladder strips. Chapple *et al*. [49••] have very recently reported their findings from an Astellas Phase IIa clinical proof of concept study. The reports are encouraging in regard to the effectiveness of YM178 in the treatment of OAB symptoms.

Rho kinase

The contractile mechanism of smooth muscle is regulated by the phosphorylation state of myosin light chain, which is in turn augmented by Rhokinase (ROCK), a downstream intermediary of the small G-protein, RhoA. Inhibitors of the RhoA/ROCK pathway have relaxant effects on smooth muscle, making it a promising target for therapeutic intervention in the treatment of detrusor overactivity [50].

Variations in RhoA/ROCK expression levels have been implicated in a number of bladder pathologies. Bing *et al*. [51] reported elevated expression of ROCK protein in detrusor muscle from decompensated bladders, using a rabbit model of partial BOO. Alterations in detrusor muscle contractile responses have been noted in the aging bladder [52] and in an in-vitro study using bladder strips from aged guinea pigs, Gomez-Pinilla *et al*. [53••] associated a loss in contractile responsiveness with decreased expression of RhoA/ROCK pathway proteins. They found that Rho/ROCK expression levels and detrusor contractile responses were greatly improved in animals treated with melatonin, a potent antioxidant.

Rajasekaran *et al*. [54] found that the ROCK inhibitor Y-27632 attenuated bladder hyperactivity in a rat model of chemical cystitis using protamine sulphate. Due to undesired hypotensive side effects, however, the clinical utility of ROCK inhibitors, such as Y-27632 and HA-1077 (fasudil), in the treatment of detrusor overactivity may be limited. The important finding of vitamin D receptor expression in human bladder smooth muscle cells [55] offers an alternative strategy. Morelli *et al*. [56••] reported that the calcitriol analogue, BXL-628 (now known as Elocalcitol; BioXell, Milan), inhibited RhoA/ROCK signaling in human bladder smooth muscle cells and promoted bladder relaxation in rats. In a recently completed phase IIa preclinical trial, Elocalcitol is reported to have significantly improved bladder storage capacity in postmenopausal women with OAB.

Botulinum toxin

Botulinum toxin type A (BTX-A) has been successfully used in a number of urologic disorders including detrusor hypoactivity, sensory disorders, interstitial cystitis and BPH [57••,58]. To date, intradetrusor injections for treatment of urinary urgency and incontinence due to intractable neurogenic or idiopathic overactivity has yielded the most promising results [59–63]. Questions still remain regarding the optimal dose and injection site for efficacy and safety [64•]. In this regard, Kuo [65••] found no difference between injecting the detrusor, submucosal or basal with respect to effect on detrusor overactivity; however, injection near the bladder base relieved urgency with no effect on bladder capacity. Further, Karsenty *et al*. [66] showed no evidence of fibrosis or vesicoureteral reflux when injecting near the trigone region. A range of reports suggest beneficial effects can last up to 6 months, with higher doses and repeat injections reported to be safe, efficacious and continue to elicit a beneficial effect over the course of several years [67–69,70•,71]. Though a urodynamic test would be useful in order to predict patient responsiveness prior to injection, it was shown that the 'ice water test' was not predictive of efficacy of botulinum toxin injections in patients with neurogenic detrusor overactivity [72].

BTX-A is now thought to have a dual mechanism of action, which involves binding to its receptor, the synaptic vesicle protein SV2 [73]. Besides targeting efferent neural pathways (blocks acetylcholine release thereby decreasing smooth muscle contractility), recent basic and clinical evidence suggests that BTX-A may inhibit sensory pathways, which may explain the beneficial effects on urgency. In support, Lucioni *et al*. [74••] showed that BTX-A inhibited release of both substance P and calcitonin gene-related peptide (likely from bladder nerves or other sensory structures) in isolated bladders from injured or inflamed rats. These findings suggest a benefit in treatment of neurogenic inflammation. Though results from available clinical trials are inconclusive, experimental data support the use of BTX-A in patients with painful bladder syndrome and interstitial cystitis [75,76]. Lui and Kuo [77] reported that BTX-A significantly reduced nerve growth factor mRNA expression, obtained from interstitial cystitis patient mucosal biopsies, and this correlated with a reduction in the associated bladder pain.

Conclusion

While most therapies have targeted bladder afferent pathways or smooth muscle, it is becoming increasingly clear that a complex 'chemical crosstalk' exists in the periphery between the bladder urothelium and other structures including neural pathways, interstitial cells and smooth muscle. While this review mainly focused on peripheral interactions/targets, recent reports have highlighted the use of nonspecific phosphodiesterase inhibitors for the treatment of neuropathic pain, by targeting 'glial' cells in the spinal cord [78••]. Though currently there is little evidence for glial cell modulation of neural excitability in bladder disorders, a recent study [79] reported altered spinal cord glial cell (morphology/staining density) in an animal model for interstitial cystitis. A better understanding of these types of interactions may open new avenues for the future clinical management of bladder dysfunctions.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 437–438).

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