*Forum Minireview*

# The Forefront for Novel Therapeutic Agents Based on the Pathophysiology of Lower Urinary Tract Dysfunction: Pathophysiology and Pharmacotherapy of Overactive Bladder

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**Abstract.** Overactive bladder (OAB) syndrome, which is characterized by a complex of storage symptoms (urinary urgency, frequency, nocturia, and urgency incontinence) is highly prevalent within the general population, causing major distress to patients in terms of their psychosocial and physical functioning. Muscarinic receptors of bladder smooth muscles are involved in both normal and disturbed bladder contraction. The muscarinic receptor functions may change in bladder disorders associated with OAB, implying that mechanisms, which normally have little clinical importance, may be up-regulated and contribute to the pathophysiology of OAB. In addition, several reports have suggested that various stimulations release many substances, including adenosine triphosphate, prostaglandins, nitric oxide, and acetylcholine, from bladder urothelium, which contribute to pathophysiology of the increased bladder sensation, OAB symptoms, and detrusor overactivity. Bladder urothelium possesses a non-neuronal cholinergic system and high density of muscarinic receptors. The roles and functions of the non-neuronal cholinergic system in OAB are now being evaluated. In the pharmacotherapy of OAB, antimuscarinic agents are the first choice drugs. Furthermore, new therapeutic targets at the levels of the urothelium, detrusor muscles, autonomic and afferent pathways, spinal cord, and brain are proposed. In this review, the pathophysiology of OAB, especially the role of non-neuronal acetylcholine, is discussed. In addition, new drugs with new action mechanisms will be introduced.

*Keywords*: overactive bladder, pathophysiology, pharmacotherapy, antimuscarinic drug, muscarinic receptor, lower urinary tract

## 1. Definition and prevalence of overactive bladder (OAB)

OAB is a symptom complex that is comprised of the storage symptoms of urgency with or without urgency incontinence, frequency, and nocturia (1). These symptoms are suggestive but not diagnostic of detrusor overactivity (urodynamically demonstrable involuntary bladder contractions) if there is no proven infection or other obvious pathology. OAB is, therefore, clearly distinct from urodynamically proven detrusor overactivity, although the majority of people with OAB are thought to have this underlying diagnosis. The prevalence of OAB increases with age. From the epidemiological studies conducted to date, it can be concluded that of those patients with OAB, approximately one-third are troubled

by incontinence (OAB 'wet') and two-thirds are not (OAB 'dry') (2, 3). The NOBLE (National Overactive Bladder Evaluation) study (3) estimated the overall prevalence of this condition in the US population to be 16% in men and 16.9% in women. As the population ages, an overall increase in prevalence occurs. A Japanese epidemiological survey (4) estimated a slightly lower overall incidence (12.4%) in the general population aged over 40, but the prevalence increased with age, with more than 20% of people older than 70 years and more than 35% older than 80 suffering lower urinary tract symptoms.

More recent data from the EPIC (European Prospective Investigation into Cancer and Nutrition) Study suggest that the prevalence of OAB symptoms [using the 2002 International Continence Society (ICS) definition] is closer to 12% in the community; and of these sufferers, approximately 50% experience significant bother from their symptoms (5).

## 2. Pathophysiology of OAB

### 2.1. Increased myogenic activity of detrusor smooth muscles

This is an important mechanism inducing OAB and detrusor overactivity, which seems to be more applicable to patients with bladder outlet obstruction (BOO). Partial BOO increases intravesical pressure and induces bladder hypertrophy and partial denervation of the bladder smooth muscle, leading to various functional changes in smooth muscles. These changes include denervation supersensitivity of cholinergic (muscarinic) receptors (6), increases in purinergic receptor–mediated contractile responses as well as expression of purinergic receptors such as $P2X_1$ (7, 8), and changes in the cell-to-cell communication in detrusor muscles due to up-regulation of gap-junction proteins such as connexin 43 (9, 10). Thus, increases in receptor-mediated muscle contractility and interaction between smooth muscles cells can result in coordinated myogenic contraction of the entire bladder and detrusor overactivity.

It has been suggested that local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated myogenic contraction of the whole bladder. This local contraction in the bladder wall has been shown to generate afferent discharge (11). Recently, localized bladder activity was assessed by the micromotion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized activity than the control group (12). This observation suggests that localized distortion of the bladder wall simulates afferent activity,

which would precipitate a feeling of urgency and detrusor overactivity.

In addition, another population of cells in the bladder known as interstitial cells has been proposed for a pace-making role in spontaneous activity of the bladder (13, 14). Because it has been reported that the number of interstitial cells is increased in a guinea-pig model of BOO (15) and that c-kit tyrosine kinase inhibitors, which inhibit interstitial cell activity, decreased the amplitude of spontaneous contractions in the guinea-pig and human bladder (16, 17), interstitial cells may also be involved in the emergence of detrusor overactivity because of enhanced autonomous detrusor muscle activity.

### 2.2. Role of urothelium and bladder afferent

The bladder urothelium has roles other than just being a barrier. There is increasing evidence that urothelial cells play an important role in modulation of bladder activity by responding to local chemical and mechanical stimuli and then sending chemical signals to bladder afferent nerves. It has been shown that urothelial cells express various "sensor molecules" such as receptors of bradykinin, neurotrophins, purines (P2X and P2Y), norepinephrine (NE) ($\alpha$ and $\beta$), ACh (nicotinic and muscarinic), epithelial $Na^+$ channels (ENaC), and a number of transient receptor potential (TRP) channels. These sensor molecules respond to mechanical as well as chemical stimuli and in turn release chemicals such as ATP, prostaglandins (PG), nerve growth factor (NGF), ACh,
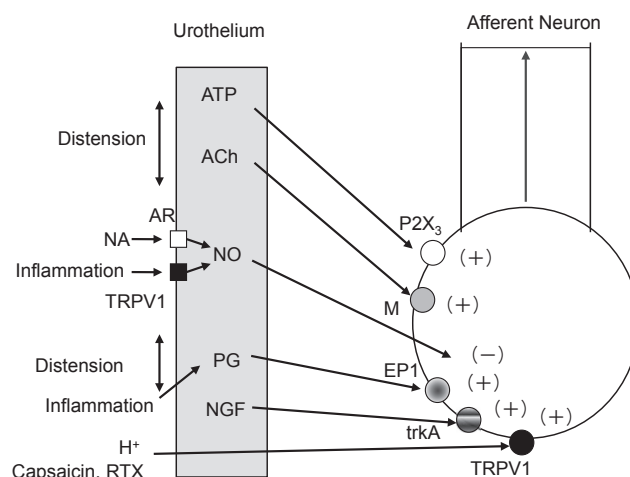


**Fig. 1.** Bladder urothelial mechanico-afferent transduction. Urothelium releases many neurotransmitters and factors due to bladder distension or various stimulations. These factors contribute to the stimulation and inhibition of afferent C neurons, suggesting the important role in the symptoms of OAB. ATP: adenosine triphosphate, ACh: acetylcholine, NA: noradrenaline, AR: adrenergic receptor, NO: nitric oxide, PG: prostaglandin, RTX: resiniferatoxin, M: muscarinic receptor, NGF: nerve growth factor.

and NO. These agents are known to have excitatory or inhibitory actions on afferent nerves, which are located close to or in the urothelium (Fig. 1).

Neural plasticity of bladder afferent pathways is also one of the mechanisms of OAB. Urothelial dysfunction that can increase the amount of urothelially released substances may lead to the changes in properties of bladder afferent pathways, resulting in increased OAB symptoms. In particular, C-fiber bladder afferents may be critical for symptom generation in pathologic states such as OAB because these fibers demonstrate remarkable plasticity: After neurologic or possibly inflammatory insult, C-fibers become the predominant afferent route carrying impulses involved in the micturition reflex to the spinal tract (18, 19).

### 2.3. Urothelial alterations in OAB

Several specific alterations in urothelial function and ultrastructure have been demonstrated in OAB. Expression of the mechanosensitive ENaC is increased significantly in human obstructed bladders in comparison with unobstructed controls and correlates significantly with storage symptom scores (20). It is possible that increased expression of mechano-sensitive channels such as ENaC in the urothelium enhances substance release upon bladder stretch. In accordance, stretch-evoked ATP release from urothelial cells is enhanced in chronic spinal cord–injured animal models (21). Release of ACh from human urothelial and suburothelial sites increases with age, as well as during bladder stretch, and represents a functional, non-neuronal, alternative cholinergic system (22). Levels of PG, which are locally synthesized in bladder muscle and mucosa, and levels of NGF are increased in subjects with OAB in comparison with controls; and in symptomatic patients, levels of $PGE_2$ are positively correlated with voiding behavior and maximum cystometric capacity (23, 24).

Overall, up-regulation of urothelial function and increased release of various chemical mediators and known neurotransmitters may influence afferent nerve activity to generate OAB symptoms, although the precise mechanism by which these processes interact with neural tissue to achieve signal transduction remains to be clarified.

### 2.4. Role of non-neuronal ACh and the muscarinic receptors

Previously, we demonstrated that non-neuronal ACh release increased and was significantly greater in stretched human bladder strips with intact urothelium, when compared with those without urothelium (22). The release was also related to age of the bladder tissue donor.

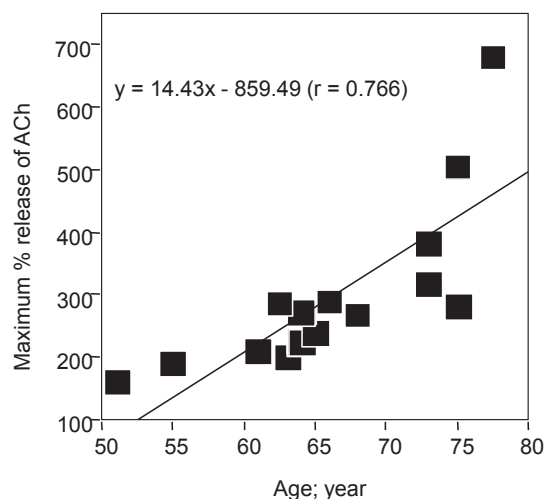In addition, non-neuronal ACh releases were gradually



**Fig. 2.** Effect of age on stretch-induced non-neuronal ACh release from human bladder strip with urothelium. Correlation between age and stretch-induced maximal percentage of release of non-nerve-evoked ACh. For measurement of non-nerve-evoked ACh, micro-dialysis procedure was performed in all bladder strips pretreated with tetrodotoxin (1 $\mu$M), under 0-mN resting tension. (Reproduced from Ref. 22 with permission)

increased according to the elevation of the resting tension by stretch of bladder strips with urothelium, and the releases were increased age-dependently (Fig. 2). It is supposed that the elevation of the resting tension of bladder strips is a similar condition to distension of bladder wall in the storage phase of the micturition cycle. Thus, it may be assumed that during the storage phase, there is an ongoing stimulation of detrusor tone by ACh released from non-neuronal sources, possibly the urothelium.

Although the exact action mechanism of non-neuronal ACh for the bladder function has not been elucidated, the muscarinic receptors–mediated mechanism in afferent neurons, myofibroblast, and urothelium might be related. For the targets of non-neuronal ACh from the urothelium, it could be expected to enhance the muscarinic receptors–mediated myogenic contractile activity of the detrusor, which has been proposed to be increased in patients with detrusor overactivity. The increased myogenic activity may, in turn, increase firing in afferent nerves and contribute to symptoms of OAB. It is also possible that non-neuronal ACh acts on afferent nerves to initiate the micturition reflex. Currently, no evidence has shown that such receptors are present on the terminals of afferents that supply the bladder. Hawthorn et al. (25) reported 1.5 times greater numbers of muscarinic receptors in the urothelium than in the smooth muscle layer in the pig bladder. A recent report (26) also demonstrated a high density of $M_2$ muscarinic receptors in the human bladder mucosa. Furthermore, Mukerji et al. (27) reported that $M_2$ and $M_3$ immunoreactive staining presented in human

detrusor, myofibroblast-like cells, nerve fiber bundle, and dorsal root ganglion of small and medium sensory neurons in the suburothelium. These muscarinic receptors might be targets of non-neuronal ACh from the urothelium.

Recently, to clarify the contribution of mucosal muscarinic receptors to bladder function, we investigated the effects of various antimuscarinic drugs on the stretch-induced non-neuronal ATP release in human bladder (28). In this study, non-neuronal ATP release from bladder strip without mucosa was about 10% of that from strip with mucosa. Non-neuronal ATP release was significantly inhibited by pretreatment with nifedipine or in $Ca^{2+}$-free medium. Both methoctramine ($M_2$ receptor–selective antagonist) and 4-DAMP ($M_3$ receptor–selective antagonist) significantly inhibited the release. However, an $M_1$ receptor–selective antagonist (pirenzepine) did not have significant effect on the release (Fig. 3A). Oxybutynin, propiverine, tolterodine, and solifenacin caused concentration-dependent inhibition in non-neuronal ATP release. The rank order of the maximum inhibition rate was propiverine $\geq$ solifenacin $\geq$ tolterodine $\geq$ oxybutynin. Solifenacin showed the inhibitory effect at lower concentration, as compared to the other drugs (Fig. 3B). The data suggest that human bladder mucosa is a main source of stretch-induced non-neuronal ATP release and that stimulation of $M_2$- and $M_3$-receptor subtypes of mucosa partly contributes to non-neuronal ATP release. Various antimuscarinic drugs used for OAB treatment may have different inhibitory effects on non-neuronal ATP release.

Muscarinic receptors are involved in both normal and disturbed contraction, and the most common drug treatment for OAB is antimuscarinic drugs. It is reported that antimuscarinic drugs act mainly during the storage phase, increasing bladder capacity and decreasing urgency, while there is normally no activity in parasympathetic nerves during the storage phase (29). However, if there is an increased non-neuronal ACh release during storage, which is proposed to be a contributing factor to OAB, it is possible that antimuscarinic drugs have some inhibitory effects on muscarinic receptors activated by the non-neuronal ACh. In addition, it will be speculated that non-neuronal ACh may stimulate muscarinic receptors on mucosa and cause the release of non-neuronal ATP in human bladder. One of the action mechanisms of antimuscarinic drugs might be the inhibitory effect on mucosal muscarinic receptors, resulting in inhibition of non-neuronal ATP release. Thus, these data may provide useful information about the action mechanism of antimuscarinic drugs during the storage phase.
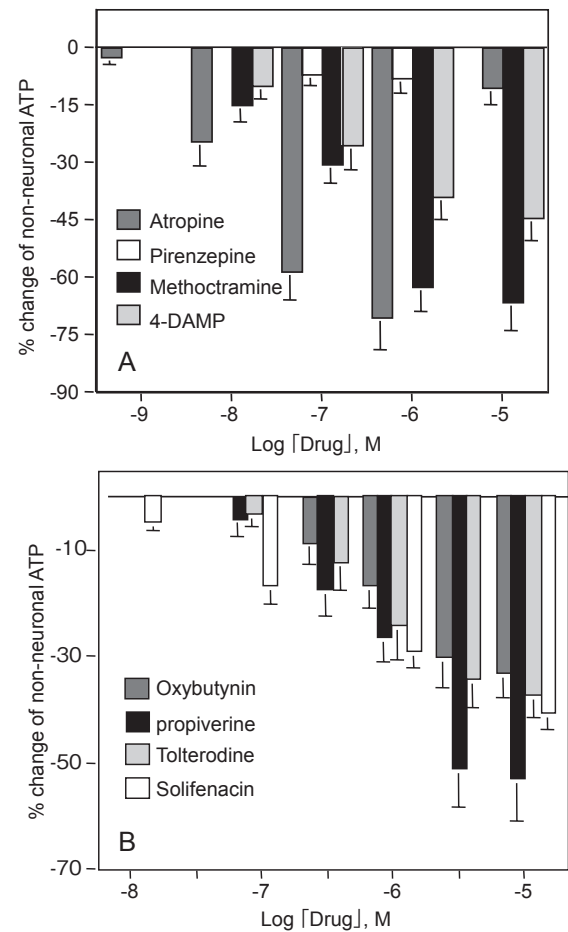


**Fig. 3.** Effects of antimuscarinic agents on non-neuronal ATP release from human bladder. A: Concentration-dependent inhibitions of muscarinic receptor selective antagonists of non-neuronal ATP release from human bladder strip with mucosa. Atropine (0.001, 0.01 – 1.0 $\mu$M: n = 8), pirenzepine (0.01 – 10 $\mu$M: n = 8), methoctramine (0.01 – 10 $\mu$M: n = 8) and 4-DAMP (0.01 – 10 $\mu$M: n = 8). B: Concentration-dependent inhibitions of various antimuscarinic agents on non-neuronal ATP releases from strips with mucosa. Oxybutynin (0.01, 0.1, 0.3, 1, 3, and 10 $\mu$M: n = 8), propiverine (0.01, 0.1, 0.3, 1, 3, and 10 $\mu$M: n = 8; tolterodine (0.01, 0.1, 0.3, 1, 3, and 10 $\mu$M: n = 8), and solifenacin (0.01, 0.1, 1, and 10 $\mu$M: n = 8). For measurement of non-neuronal ATP, microdialysis procedure was performed in all bladder strips pretreated with tetrodotoxin (1 $\mu$M), and 40 mN resting tension. (Reproduced from Ref. 28 with permission)

## 3. Pharmacotherapy

There are a number of pharmacological mechanisms that could reduce overactivity of the detrusor muscle. However, the only approved treatments with Grade A recommendation based on level 1 evidence are antimuscarinic drugs (30). An extensive literature base has demonstrated acceptable efficacy, safety, and improvements in quality of life in randomized controlled trials

for the antimuscarinic drugs (tolterodine, trospium, solifenacin, and darifenacin), drugs with mixed actions (oxybutynin and propiverine), and the vasopressin analogue desmopressin (for nocturia) (31). However, muscarinic receptors are not exclusively found in the urinary tract, but are also present in salivary glands (muscarinic $M_1$- and $M_3$-receptor subtypes), gastrointestinal smooth muscle (muscarinic $M_2$- and $M_3$-receptor subtypes), eyes (muscarinic $M_3$- and $M_5$-receptor subtypes), heart (muscarinic $M_2$-receptor subtype), and brain (muscarinic $M_1$-, $M_3$-, $M_4$-, and $M_5$-receptor subtypes). This widespread distribution of muscarinic receptors within the body is related to the commonly observed side-effects of these agents, including dry mouth, constipation, blurred vision, tachycardia, and cognitive problems (31). To avoid these side effects, the development of new therapeutic drugs is ongoing.

Potassium-channel openers have failed to show any efficacy (32). Aprepitant, an NK-1–receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting (33) significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), as shown in a well-designed pilot randomized controlled trials (34).

The effective alternative class of agents to the antimuscarinics with proven efficacy and acceptable tolerability are the $\beta_3$-adrenoceptor agonists (35). The detrusor muscle containing $\beta$-ARs and three subtypes ($\beta_1$, $\beta_2$, and $\beta_3$) have been identified in most species (36, 37). The human urothelium also contains all three receptor subtypes (38). Studies using real-time RT-PCR have revealed a predominant expression of $\beta_3$-AR mRNA in human detrusor muscle (37, 39), and the functional evidence for an important role in both normal and neurogenic bladders is convincing (37, 40 – 47). A number of $\beta_3$-AR–selective agonists, including GW427353, YM178, and KUC7483, are currently being evaluated as a potential treatment for OAB in humans (48).

Vanilloid receptor agonists capsaicin and resiniferatoxin have proven efficacy but are associated with adverse events such as urinary retention, limiting their more widespread applicability (49). Botulinum toxin A, although not approved for use in OAB and detrusor overactivity in most countries, has a well-documented therapeutic effect in neurogenic detrusor overactivity, and it may also be useful for idiopathic detrusor overactivity. It has largely replaced the vanilloids as therapeutic alternatives. However, there are not data from large-scale randomized controlled trials. It has an associated urinary retention rate and suffers an absence of long-term data associated with its use (50).

Future promising drugs for OAB include phospho-diesterase inhibitors, gonadotropine-releasing–hormone antagonists, vitamin D3–receptor analogues, EP-1–receptor antagonists, TRPV1-receptor antagonists, drugs with central mode of action (gabapentin: one of the new first-generation antiepileptic drugs, etc.) (51).

## 4. Conclusions

The pathophysiology of OAB is multifactorial. Recently, many evidences suggested the important role of urothelium in the mechanism of OAB and detrusor overactivity. Although antimuscarinic drugs are still the mainstay for treatment of OAB, development of several drugs with different mechanisms will be promising in the near future.

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