

# Pathophysiology of Overactive Bladder: Current Understanding

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## Abstract

**Purpose of Review** To describe leading hypotheses surrounding the pathophysiology of overactive bladder (OAB), as well as describe the mechanisms of action of current treatment options for OAB.

**Recent Findings** There are two main underlying mechanisms of OAB: mechanisms with increased sensory (afferent) activity and mechanisms with abnormal management of afferent signals. In the former category, increased afferent activity is thought to be related either to abnormalities in the urothelium receptor function and neurotransmitter release (urothelium-based hypothesis) or to abnormalities in myocyte excitability (myogenic hypothesis). In the latter category, OAB is thought to be related to the dysregulation of the handling of afferent signals (neurogenic hypothesis).

**Summary** OAB is complex and multifactorial in its etiology. Further research should be undertaken to better characterize the pathophysiology of the disorder, so that more targeted treatments can be developed.

**Keywords** Overactive bladder · Urinary frequency · Urinary urgency · Urinary incontinence

## Introduction

Overactive bladder (OAB) syndrome is defined by the International Continence Society (ICS) as “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology” [1]. OAB is classified as a syndrome without a known cause after local abnormalities have been ruled out by diagnostic evaluation [2–4]. It has been estimated that OAB and urinary incontinence affect up to 43% of the population; as many as 33 million people in the USA suffer from the condition, with up to 12% experiencing urinary urgency incontinence (UUI) [5–7]. The constellation of symptoms that constitute OAB often negatively affects patients’ quality of life, impacting self-esteem, interpersonal and sexual relations, as well as their lifestyle and professional lives [6].

Urodynamics may be used to evaluate patients with OAB, and detrusor overactivity (DO), a urodynamic finding, is often seen. However, DO is not found in every patient with the symptom complex, although it has been found to be more common in patients with urgency incontinence than in those without associated incontinence [8]. In those with incontinence, DO has been found to be present in 90% of men and 58% of women. Without incontinence, the rates drop to 69% of men and 44% of women with DO [6]. DO is therefore not necessary to make the diagnosis of OAB, and the patient’s history is often enough to drive its evaluation and treatment.

Currently, OAB is considered idiopathic in origin, and the pathophysiology of OAB is the subject of ongoing research. The ICS divides the underlying mechanism of OAB into two categories: mechanisms with increased sensory (afferent) activity and mechanisms with abnormal management of afferent signals [9, 10]. Increased afferent activity is thought to be related either to abnormalities in the urothelium receptor function and neurotransmitter release (urothelium-based hypothesis) or to abnormalities in

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myocyte excitability (myogenic hypothesis). In the second mechanism, in which there is dysregulation of the handling of afferent signals (neurogenic hypothesis), it is proposed that there is a defect in the central inhibitory pathways or inappropriate activation of voiding reflexes [9•, 10•]. Because OAB symptoms may also be seen in patients with neurological disease, often manifesting with DO on urodynamics [9•], a neural component may result in abnormalities of both sensory and motor pathways.

### Physiology of Normal Micturition

The bladder is dedicated to both the storage and emptying of urine. Under ideal physiological conditions, voiding occurs as a response to afferent signals from the bladder, controlled by circuits in the brain and spinal cord [11]. Once micturition occurs, coordination of neural pathways must coordinate with the smooth muscle of the detrusor and urethra, as well as the striated muscle of the urethral sphincter and pelvic floor muscles [11]. Peripheral nerve circuits therefore involve autonomic (parasympathetic and sympathetic) and somatic pathways in order to facilitate storage and emptying [12, 13, 14•].

The voiding reflex in normal adults is under voluntary control via the periaqueductal gray (PAG) and the pontine micturition center (PMC) [14•]. The PAG receives the afferent signals from signals arising from the bladder, which then stimulate the PMC to activate the voiding reflex. During filling, the prefrontal cortex suppresses the PAG in order to prevent micturition until a perceived socially acceptable time to void.

Sympathetic innervation originates from the thoracolumbar region of the spinal cord from T10 to L2, where they contribute to the superior hypogastric plexus and hypogastric nerves. Parasympathetic innervation arises from the S2 to S4 spinal cord segments, which ultimately lead to the inferior hypogastric plexus. Parasympathetic postganglionic neurons release acetylcholine (ACh) at the level of the bladder, which in turn stimulates M<sub>3</sub> muscarinic receptors in the detrusor muscle, leading to bladder contraction and emptying. Conversely, sympathetic neurons from the hypogastric nerve release noradrenaline, activating  $\beta_3$  adrenergic receptors, relaxing the smooth muscle, and facilitating storage of urine. Concomitantly, somatic axons arise from the pudendal nerve release ACh, which contracts the striated muscle of the external sphincter.

The bladder is thought to be an integrated stretch receptor organ, using a combination of afferent signals, myofibroblasts, and urothelium [15]. Bladder fullness is sensed primarily by afferent  $\alpha\beta$  fibers in the detrusor muscle [3, 16]. Unmyelinated C fibers are found in the lamina propria and urothelium and are activated in response to noxious stimuli, such as temperature change, pain, or chemical irritation.

### Urothelium-Based Hypothesis of OAB

Combined with the underlying suburothelium, which is composed of nerves, blood vessels, and connective tissue, the urothelium has widely been credited as modulating bladder activity [17]. The urothelial cells react to mechanical and chemical stimuli through various receptors, stimulating nearby afferent nerves. The urothelium expresses receptors to bradykinin, purines, norepinephrine, and acetylcholine (ACh), as well as transient receptor potential (TRP) channels, amongst others [18•]. Once the urothelium and suburothelium are activated, there is increased release of ATP, prostaglandins, NGF, ACh, nitric oxide, as well as various other chemical mediators and neurotransmitters that can affect efferent nerves.

Any abnormal activity or signaling arising in the urothelium may then lead to involuntary contractions and OAB symptoms, although the precise mechanisms must still be delineated [18•].

### Myogenic Hypothesis of OAB

Bladder function is dependent on the coordinated interaction of the nervous system with the smooth muscle cells in the detrusor. Dysfunction of the myocytes in the detrusor muscle may result in increased excitability, leading to the symptoms seen in OAB [19•, 20]. Myocytes from the bladders of patients with DO have been shown to have an increased excitability and an exaggerated response to stimuli [19•].

Drake et al. [21] theorized that the detrusor muscle is arranged into modules which are controlled by a peripheral myovesical plexus. As a result, any local activity within the detrusor muscle may extend to a coordinated response throughout the bladder wall. Increased excitability of the detrusor muscle may arise as a result of partial denervation of the detrusor and altering of the smooth muscle [22]. The modules may therefore develop an amplified response to stimuli as well as associated feelings of urgency [23–26].

Coupling of bladder smooth muscle cells occurs via gap junction channels, which are primarily made up of connexins. Within the detrusor muscle, Cx43 and Cx45 are most prominent [27, 28], and it has been shown that there is an increase in Cx43 expression in patients with neurogenic DO and urinary symptoms [28, 29]. Current studies continue to explore the role of connexins in the pathophysiology of OAB.

Additional research is ongoing to investigate the role of the interstitial cells in the bladder as potential pacemakers of detrusor muscle contractions [30, 31].

### Neurogenic Hypothesis of OAB

Any insult to the central nervous system has the ability to disrupt normal micturition control and cause reflex

micturition, depending on the location and severity of the injury [32]. The neurogenic hypothesis asserts that DO is related to inappropriate excitation of the detrusor during the storage phase of micturition due to aberrant CNS activation [33]. Neurogenic detrusor overactivity (NDO) is thought to be an abnormality in the central inhibitory pathway and/or inappropriate activation of voiding reflexes [14].

For suprapontine lesions, cortical lesions may damage cerebral inhibitory centers [19]. Hence, OAB is prevalent after cerebrovascular accidents. Cerebral infarction may also lead to the induction of several factors which cause OAB, including N-methyl-D-aspartic acid (NMDA) glutamatergic mechanisms, dopamine D2 receptor excitatory mechanisms, and nitric oxide [3]. Patients with Parkinson's disease also often have OAB symptoms; the basal ganglia normally help to inhibit voiding, and with the degeneration of the substantia nigra in Parkinson's, OAB symptoms often ensue. Furthermore, OAB is common in multiple sclerosis due to demyelinating plaques of the brain and spinal cord, notably the posterior and lateral columns of the cervical spinal cord, affecting the neural pathways between the brain and bladder.

For lesions that occur above the lumbosacral spinal cord, voluntary micturition may be disrupted, resulting in an areflexive bladder resulting in urinary retention [34]. Unmyelinated C fibers help mediate the sacral spinal reflex, which is activated by bladder filling at low volumes, causing NDO. Detrusor sphincter dyssynergia (DSD) can also be seen, in which contractions of both the bladder and external sphincter occur, resulting in high bladder pressures that may threaten the upper urinary tract.

### Integrative Hypothesis of OAB

Due to the complexity of mechanisms involved in micturition, it is likely that each of the hypotheses plays a role in the pathophysiology of OAB. The integrative hypothesis encompasses each of the components; there are a range of potential triggers that can induce localized detrusor contractions (micromotions) which are then propagated to the bladder wall [23]. As a result, the sense of urgency can then arise [21]. The finding of DO on urodynamics will be manifested when exaggerated micromotions lead to a contraction of the bladder muscle.

### Treatments of OAB

Based on the proposed hypotheses, various treatment options are available for OAB.

The goal of management is to optimize continence, minimize complications (such as infections), and improve the patient's quality of life. Initial workup should include a thorough voiding history and medical evaluation, as well as a physical

exam to assess for urinary incontinence and pelvic organ prolapse that may also contribute to their symptoms. It is important to rule out chronic urinary tract infections and urinary retention during the initial evaluation, and to evaluate for neurologic or medical related conditions that may also play a role. Urodynamics, with or without fluoroscopy, can play a role for patients with a complicated urological or neurological history, and for those who fail conservative management.

General lifestyle changes should be recommended as a first-line treatment in all patients with OAB, which include limiting fluid intake to 1-2 liters a day, eliminating caffeine, timed voiding, and pelvic floor exercises. Pelvic floor muscle training (PFMT) may enhance the inhibitory effect of pelvic floor contraction on the detrusor, thus improving urgency and urge-related incontinence [35]. Bladder training, which involves incrementally delaying urination for longer periods of time, can further improve detrusor overactivity [36].

Medications, including antimuscarinics and  $\beta_3$  adrenergic agonists, are the mainstay treatment options for OAB, based on both theoretical efficacy and clinical experience. Antimuscarinic medications act by blocking the muscarinic receptors on the detrusor muscle, preventing the bladder from contracting. Interestingly, the medications act during the storage phase when there is minimal parasympathetic input to the lower urinary tract [37, 38]. Furthermore, despite being competitive antagonists, antimuscarinics do not significantly reduce contractions at the time of voiding [39]. Antimuscarinics may be efficacious in the treatment of OAB as a result of decreasing the activity in afferent nerves from the bladder [40, 41].

$\beta_3$  adrenergic agonists are thought to lead to relaxation of the detrusor muscle by directly stimulating the  $\beta_3$  adrenergic receptors, leading to increased levels of adenylyl cyclase and cAMP [42]. However, it has been shown that stimulation of the bladder  $\beta_3$ -ARs may activate plasma membrane K<sup>+</sup> channels, reducing membrane excitability and inhibiting both myogenic and neurogenic contractions in the detrusor muscle [43]. Furthermore, there is growing evidence that the effect of  $\beta_3$ -AR activation on parasympathetic neurons may inhibit acetylcholine release, leading to a reduction of detrusor contractions [44].

In patients who fail behavioral modifications and medical therapy, percutaneous tibial nerve stimulation (PTNS) has been shown to be effective in the treatment of OAB. The posterior tibial nerve originates from spinal roots L4 to S3 and has both sensory and motor nerve-containing fibers that innervate the pelvic floor muscles, bladder, and sphincter. It is electrically stimulated using a needle electrode placed cephalad to the medial malleolus for repeated sessions of 30 min each. Although the mechanism of action is not clearly understood, there is evidence that activation of somatic sacral afferent nerves affects both storage and emptying reflexes in the bladder [33, 45, 46]. Multiple randomized controlled studies have demonstrated a reduction in OAB symptoms as well as

improvement in urodynamic parameters [47–49] with PTNS treatment, although duration of efficacy is limited.

In a similar vein, sacral neuromodulation has gained widespread use for the treatment of refractory OAB. In 1997, the Food and Drug Administration approved medtronic bladder control therapy (the InterStim System) for the treatment of urinary urgency and frequency. The InterStim device consists of a small lead wire that is placed along the S3 nerve, which is then stimulated through a pulse generator. Although its mechanism of action is incompletely understood, it likely interferes with abnormal reflex arcs, which control the symptom patterns at the sacral nerve roots S3 and S4. Multiple prospective trials have shown a greater than 50% decrease in intractable urinary symptoms and incontinence episodes with the use of InterStim [50–52].

Several well-designed studies have evaluated the use of intravesical injections of OnabotulinumtoxinA for the treatment of OAB, all of which reported significant improvement of urinary symptoms [53–55]. Considered a third-line treatment for OAB [56], OnabotulinumtoxinA is a neurotoxin derived from *Clostridium botulinum*, which is injected into the bladder wall cystoscopically. It is thought to inhibit release of Ach from presynaptic neurons, as well as ATP and substance P from the urothelium, thereby leading to paralysis of the detrusor muscle [57]. It may also act on C-fiber afferents leading to a reduction in the sense of urgency [57–59]. Although the treatment effect lasts anywhere from 6–8 months, multiple injections continue to be safe and effective [60], and it has proven to be a novel therapy for OAB.

## Conclusion

Overactive bladder (OAB) syndrome encompasses a complex array of urinary symptoms, with urinary urgency being the predominant feature. Currently, OAB is considered idiopathic in origin, although multiple hypotheses have been proposed to explain its development. The underlying mechanism of OAB can be divided into two categories: mechanisms with increased sensory (afferent) activity and mechanisms with abnormal management of afferent signals. Within the first category, increased afferent activity is thought to be related either to abnormalities in the urothelium receptor function and neurotransmitter release (urothelium-based hypothesis) or to abnormalities in myocyte excitability (myogenic hypothesis). In the second mechanism, it is proposed that there is a defect in the central inhibitory pathways or inappropriate activation of voiding reflexes (neurogenic hypothesis) that lead to OAB symptoms. It is likely that OAB is a result of each of these mechanisms (integrative hypothesis), given the efficacy of the varied treatment options.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Palmer and Dr. Choi declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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