Pathophysiology of Overactive Bladder and Urge Urinary Incontinence

William D. Steers, MD, FACS
Department of Urology, University of Virginia, Charlottesville, VA

Storage symptoms such as urgency, frequency, and nocturia, with or without urge incontinence, are characterized as overactive bladder (OAB). OAB can lead to urge incontinence. Disturbances in nerves, smooth muscle, and urothelium can cause this condition. In some respects the division between peripheral and central causes of OAB is artificial, but it remains a useful paradigm for appreciating the interactions between different tissues. Models have been developed to mimic the OAB associated with bladder instability, lower urinary tract obstruction, neuropathic disorders, diabetes, and interstitial cystitis. These models share the common features of increased connectivity and excitability of both detrusor smooth muscle and nerves. Increased excitability and connectivity of nerves involved in micturition rely on growth factors that orchestrate neural plasticity. Neurotransmitters, prostaglandins, and growth factors, such as nerve growth factor, provide mechanisms for bidirectional communication between muscle or urothelium and nerve, leading to OAB with or without urge incontinence. [Rev Urol. 2002;4(suppl 4):S7–S18]

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Patients with an unstable bladder are defined urodynamically as demonstrating an uninhibitable elevation in intravesical pressure during bladder filling. These patients often share common symptoms, including urgency, frequency, urge incontinence, and nocturia, regardless of etiology. Urodynamics fails to discriminate among idiopathic, myogenic, and neuropathic causes. Moreover, 10%–45% of individuals with unstable bladder contractions may be asymptomatic.
The bladder may be capable of only a limited repertoire of behaviors in response to disease. If that is the case, very different pathologic mechanisms may manifest as the same symptom. Yet the similarity of the symptoms suggests that common factors may underlie the instability. Shared traits exhibited by unstable bladders from humans and those from animals include increased spontaneous myogenic activity, fused tetanic contractions, altered responsiveness to stimuli, and characteristic changes in smooth muscle ultrastructure (Figure 1). Examination of the peripheral innervation and the micturition reflex in models of OAB reveals consistent changes that include patchy denervation of the bladder, enlarged sensory neurons, hypertrophic ganglion cells, and an enhanced spinal micturition reflex. These shared features make it plausible that regardless of the etiology, the underlying causal mechanisms are similar.

**Electrical Properties of Unstable Detrusor**

Smooth muscle from unstable bladders often shows enhanced spontaneous contractile activity. This has been documented in human bladder strips from obstructed unstable bladders and those patients with neuropathy. Altered responses are also seen to stimulation of the unstable detrusor with agonists and to electrical stimulation. Yet there are subtle differences depending on etiology in the patterns exhibited in tissues from unstable bladders. Obstructed bladders are supersensitive to muscarinic agonists and potassium chloride (KCl) (Figure 2). On the other hand, the obstructed detrusor has reduced contraction on nerve stimulation. In idiopathic instability, bladder strips show supersensitivity to KCl but not to muscarinic agonists, and reduced contractile response to electrical stimulation. Unstable strips may even be more easily activated by direct electrical stimulation of the smooth muscle, showing contractions elicited by stimulation of nerves that are resistant to the nerve-blocking action of tetrodotoxin (TTX).

Smooth muscle bundles in normal detrusor are not as well coupled electrically as those in most viscera. Absent coupling implies that in vivo electrical activity can traverse the length of individual cells without the risk of inadvertently spreading and raising intravesical pressure. To compensate for the absence of coupling, dense innervation allows synchronous activation of the muscle and a rise in intravesical pressure during volitional voiding.

Compared to normal bladders, unstable bladders are better coupled electrically. This allows spontaneous electrical activity to spread and initiate synchronous contractions throughout the detrusor, which explains the fused tetanic contractions seen in unstable bladder strips. In the whole bladder, the increased excitability and greater connectivity of the smooth muscle create foci of electrical activity that could propagate and generate an uninhibited contraction.

**Morphologic Changes in the Detrusor**

Regardless of the etiology, unstable detrusor develops common changes in the macroscopic structure of the bladder. Unstable human bladders frequently show patchy denervation of the muscle bundles. Some muscle...
fascicles may be completely denervated, while neighboring bundles appear normal. Other regions may show intermediate innervation. After complete denervation, hypertrophy of the smooth muscle cells occurs. At an ultrastructural level, a common feature in unstable detrusor is the presence of protrusion junctions and ultra-close abutments between the myocytes. This picture is rare in the normal detrusor and may represent the morphologic correlate to increased electrical coupling in unstable bladders.

Neuroplasticity
While myogenic mechanisms are in place to ensure that an inadvertent neural impulse does not trigger a detrusor contraction, the nervous system is designed to ensure that transmission occurs across synapses with a high degree of efficiency. Furthermore, the default mode seems to be to empty the bladder in response to injury or disease, consistent with a role in eliminating toxic waste. The ability of the nervous system to change transmitters, reflexes, or synaptic transmission with disease, injury, or changes in the environment involves neuroplasticity. On the one hand, plasticity may shift the balance toward voiding. However, coexistent conditions such as ischemia may injure nerves so sensation is lost or damage to smooth muscle results in impaired contractility. The net effect could be clinical scenarios such as detrusor hyperactivity with impaired contractility (DHIC) or unstable contractions in the absence of sensation of urgency.

The concept of such a relationship among ischemia, obstruction, aging, and OAB is supported by a recent investigation demonstrating that blood flow to the detrusor smooth muscle was reduced in proportion to the level of decompensation. Ischemia, aside from initiating apoptosis of smooth muscle cells, damages intrinsic nerves. Neurons are more susceptible to ischemia than smooth muscle, and such damage is irreversible. Neuronal degeneration is common in obstructed unstable bladders and may contribute to instability.

The patchy denervation suggests the death of some of the intrinsic bladder neurons. Bladder ischemia may occur with severe obstruction or from peripheral vascular disease. In the hypertrophied detrusor following obstruction, increased metabolic demands combined with reduced blood flow can produce anoxia, triggering neuronal death. This could result from obstruction due to benign prostatic hyperplasia (BPH), urethral stricture, or detrusor-sphincter dyssynergia.

Spinal cord transection and urethral obstruction produce bladder instability and an increase in size of both the afferent neurons in the dorsal root ganglia (DRG) and the efferent neurons in the pelvic plexus (after obstruction). After spinal injury, electrophysiologic measure-
ments reveal a shorter delay in the central transmission of the micturition reflex.\textsuperscript{15,16} The micturition pathway is reorganized from a spinobulbospinal loop to a predominantly spinal network. Silent C-fiber (unmyelinated) afferents can trigger micturition in unstable bladders, although not in normal bladders. Such reorganization probably occurs in humans, because the ice water test that activates specific cold-sensitive C-fibers fails to evoke micturition in normal subjects but does so in obstructed and neuropathic patients.\textsuperscript{17,18} Moreover, intravesical administration of selective C-fiber neurotoxins such as capsaicin and resiniferatoxin often eliminates instability.\textsuperscript{19} It is plausible that the changes associated with OAB are the result of alterations in activity in the nerves controlling the detrusor.

Clinical observations provide a hint that urgency is a separate sensation from that of bladder fullness. Recordings from afferents during bladder filling and contraction\textsuperscript{20,21} have shown increased activity in a unimodal population of small myelinated and unmyelinated (A-delta and C) fibers in response to intravesical pressure and contraction (Table 1). This implies that there are in-series stretch receptors in the bladder wall whose activity correlates with the sensations of bladder filling and fullness. However, it seems unlikely that fibers with such properties normally mediate the sensation of urgency. Normally the urgent desire to void disappears once voiding begins. Unstable pressure rises may also appear in the absence of sensation. It has been postulated that urgency is triggered by local distortions in the bladder wall, caused by heterogenous activity in some muscle bundles.\textsuperscript{22} This scenario could develop in normal bladders if a few low-threshold postganglionic parasympathetic neurons were activated by autonomous reflex at the termination of filling. Poor coupling between bundles in normal bladder ensures that such diffuse activity does not raise intravesical pressure. However, it might elicit enough local distortions to activate a subset of nerves that specifically transduce the sensation of urgency. Enhanced coupling in the unstable bladder might permit a wave of diffuse activity, causing urgency and culminating in an involuntary contraction. If coupling is absent, then urgency exists without an intravesical pressure deviation. This hypothesis would explain the efficacy of antimuscarinic drugs in urge incontinence. If only a fraction of ganglia were activated directly by the sensory nerves, suppression of their effects could eliminate both urgency at low volumes and the unstable contractions. Urgency could also result from a lowering of the threshold or spontaneous firing of afferents, as seen in interstitial cystitis (IC) and sensory urgency.

The molecular trigger for changes in the afferents or synaptic transmission in the central nervous system (CNS) may be nerve growth factor (NGF), in addition to other neurotrophins (brain-derived neurotrophic factor, neurotrophins 3 and 4, glial-derived neurotrophic factor [GDNF]) and cytokines (Figure 3). NGF is

<table>
<thead>
<tr>
<th>Channel</th>
<th>Previous Name</th>
<th>Gene Symbol</th>
<th>Chromosome (human)</th>
<th>Pharmacology</th>
<th>KO Phenotype</th>
<th>Abundance in Adult DRG</th>
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<td>Type I</td>
<td>SCN1A</td>
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<tr>
<td>Na\textsubscript{v}1.3</td>
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<td>2q24</td>
<td>TTX-s</td>
<td>Present</td>
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<tr>
<td>Na\textsubscript{v}1.4</td>
<td>SkM</td>
<td>SCN4A</td>
<td>17q23–25</td>
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<td>Present</td>
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<td>SCN5A</td>
<td>8p21</td>
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<td>SCN9A</td>
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<td>SNS/PN3</td>
<td>SCN10A</td>
<td>3p21–24</td>
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<td>Na\textsubscript{v}1.9</td>
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<td>SCN11A</td>
<td>3p21–24</td>
<td>TTX-r</td>
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<td>Na\textsubscript{v}</td>
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<td>SCN6A/7A</td>
<td>2q21–23</td>
<td>TTX-r</td>
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</tr>
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</table>

TTX-s, TTX-r, tetrodotoxin-sensitive, -resistant.
responsible for the growth and maintenance of sympathetic and sensory neurons and has been shown to be responsible for neuronal regrowth after injury. NGF is elevated in the bladders of some models of OAB and in those of patients with BPH or IC and idiopathic detrusor instability. In animal models of partial urethral obstruction, chemical cystitis, and spinal cord injury (SCI), pretreatment with antibodies against NGF or its receptor prevents urinary frequency and unstable contractions (Figures 4 and 5). Conversely, intravesical NGF causes unstable detrusor contractions. Gene therapies delivering NGF reverse sensory defects in animal models of diabetes. Blockade of NGF also prevents shared features of neuroplasticity, such as enhanced reflex activity, increased growth-associated protein 43 (GAP-43) expression in the dorsal horn of the spinal cord, and hypertrophy of DRG neurons, in these models. Taken together, these observations suggest that NGF orchestrates some of the neuronal events leading to OAB.

Molecular Basis for Plasticity Due to NGF: Sodium Channel Isoforms

How could NGF produced by a target tissue, as in SCI, obstruction, and inflammation, and then retrogradely transported to the DRG lead to OAB? Recent data suggest that membrane conductance and thus excitability of DRG neurons are altered in models associated with increased access to NGF.
as with reawakening of C-fibers, they use their Na⁺ channels differently. But does DRG express a different repertoire of Na⁺ channels? There is extensive evidence to suggest that α subunits forming the pore of the Na⁺ channel change in response to environmental conditions and changes in access to NGF. This scenario has been called environmental plasticity associated with channelopathy.

Afferents are the early warning system for the bladder. Yet a substantial number fail to respond to normal environmental stimuli: 61% of sensory nerves innervating the rat bladder are unmyelinated C-fibers, according to findings based on conduction velocities of single dorsal root fibers. The remaining nerves are lightly myelinated A-delta fibers. While 61% of bladder afferents (both A-delta and C) respond to distention of the bladder, no less than a third fail to respond to any mechanical or chemical stimuli. It is tempting to speculate that some forms of OAB derive from recruitment of silent C-fiber afferents. The early warning system is put on full alert.

Understanding the switch from quiescent to activated afferents may be the key to understanding OAB and why anticholinergic drugs are not uniformly effective in treating urgency, frequency, and urge incontinence.

Thirty percent of DRG neurons give rise to A-delta fibers that exhibit predominantly TTX-S Na⁺ currents and are responsible for normal voiding. These cells show low thresholds and short-duration action potentials. At least 60% of bladder DRG neurons are capsaicin sensitive and express the vanilloid receptor (VR-1) (Table 2). Of these DRG neurons, 95% give rise to C-fibers.24 The TTX-R Na⁺ currents are present in small DRG neurons that are immunoreactive for sub-

Figure 5. After transient environmental (ie, intravesical) changes such as inflammation or temporary obstruction, afferents may revert to normal activity. However, if patient is genomically predisposed to OAB (eg, exhibits familial urge incontinence or chronic pain syndromes such as interstitial cystitis, irritable bowel syndrome, or fibromyalgia) or long-term environmental changes occur, nerve growth factor (NGF) may alter afferents irreversibly. Antibody to NGF or fusion protein against the NGF receptor prevents overactive bladder (OAB) in animal models coincident with alterations in afferents. NGF’s long-term actions may rely on changes in sodium (Na⁺) channel isoforms expressed by afferents that influence excitability. Most unmyelinated (C-fiber) afferents are not responsive to normal stimuli such as distention or presence of intravesical contents. However, following spinal cord injury, obstruction, or inflammation, activation of the silent C-fibers occurs. The reawakening of silent C-fibers may correspond to changes in Na⁺ channel expression. Novel approaches to OAB in the future may target the mechanisms leading to these long-term changes. Reprinted from Morrison J, Steers WD, Brading A, et al. Neurophysiology and neuropharmacology. In: Khoury S, Abrams P, Wein A (eds). Incontinence, 2nd ed. Plymouth, UK: Health Publication Ltd; 2002.
stance P and calcitonin gene-related peptide (SP/CGRP), express trk-A, and give rise to C-fibers supplying the bladder.24,25 More than 85% of Na’ currents in small-diameter (C-fiber) DRG neurons corresponding to bladder retrogradely labeled cells exhibit predominantly TTX-R currents. These TTX-R cells demonstrate high thresholds and long-duration action potentials and likely contribute to the higher thresholds for C-fibers. After SCI, obstruction, or cystitis, enhancement of spinal reflexes has been confirmed by abolishment with capsaicin and a positive ice-water test clinically.26 Plasticity occurs in TTX-S and TTX-R Na+ channels as well as in potassium (K+) channels in DRG neurons after SCI, obstruction, or cystitis. With SCI, 60% of dissociated bladder DRG neurons exhibit TTX-S Na+ currents, compared to 30% of such neurons in intact rats.27 IA K+ (low-conductance potassium) currents are also postulated to be reduced, preventing membrane relaxation. These two changes lead to enhanced excitability of C-fibers coinciding with development of a spinal micturition reflex. With cyclophosphamide cystitis, slowly inactivating IA currents in TTX-R neurons are reduced, possibly leading to OAB.27 As further evidence for a channelopathy contributing to OAB, antisense but not sense deoxyoligonucleotides against the (Na1.8) Na’ channel (TTX-resistant) reduce urinary frequency and unstable contractions in cyclophosphamide cystitis and bladder outlet obstruction and, in a model of idiopathic instability/attention deficit disorder/hypertension, the spontaneously hypertensive rate (SHR).28,29 It is tempting to speculate that the cellular basis for this plasticity is a change in Na’ currents. The molecular basis for this plasticity may be a change in the expression or function of Na’ and K’ channel isoforms. The trigger for plasticity may be NGF or other signaling molecules.

There is clinical evidence that Na’ channels play a role in OAB and can be manipulated to treat urgency and frequency. The local anesthetic and nonselective Na’ channel blocker lidocaine can be used to reduce the symptoms of OAB in a variety of conditions, including BPH. Intravesical lidocaine blocks sensory nerve transmission from the human bladder; like subcutaneous lidocaine, it may preferentially act on C-fibers. These are the afferents that give rise to pathologic reflexes such as the ice-water test.30 Intravesical lidocaine increases bladder capacity and reduces involuntary contractions. In a small, uncontrolled study of elderly patients with detrusor instability, the oral Na’ channel blocker mexiletine improved or cured urge incontinence.31 The effects of these agents vary with the disease. Perhaps alterations in Na’ channel expression within nerves are limited to certain types of conditions leading to OAB. Differences in degree of innervation or access to drug could explain differential actions of nonselective local anesthetics that block Na’ channels. In children with neurogenic bladders due to myelodysplasia, Lapointe and colleagues32 found that intravesical lidocaine decreased involuntary contractions in 58% of patients, but increased capacity in 71% of subjects by nearly 60%. Lidocaine increases bladder capacity to the greatest degree in spinal cord–injured patients (230%) compared to its effect in supraspinal neurologic conditions and BPH.33 The first of these conditions is associated with a C-fiber reflex. A reduction in involuntary detrusor contractions is seen only in the first two conditions but not in

<table>
<thead>
<tr>
<th>Peptidergic</th>
<th>Nonpeptide</th>
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<tbody>
<tr>
<td>NF – 60% bladder C-fibers</td>
<td>NF- 10% bladder C-fibers</td>
</tr>
<tr>
<td>IB4 – SP/CGRP</td>
<td>IB4/FRAP +</td>
</tr>
<tr>
<td>Trk A-NGF responsive</td>
<td>Trk B-BNDF responsive</td>
</tr>
<tr>
<td>VR1</td>
<td>VR1/P2X3</td>
</tr>
<tr>
<td>Laminae I/II</td>
<td>Inner laminae II</td>
</tr>
<tr>
<td>Projection 2nd order to brainstem/thalamus</td>
<td>2nd order interneurons in spinal cord</td>
</tr>
</tbody>
</table>

| NF, neurofilament; IB isolecint; SP, substance P; CGRP, calcitonin gene-related peptide; VR, vanilloid receptor; FRAP, fluorescent acid phosphatase; Trk, tyrosine kinase receptor; P2X3, P2X3 purinergic receptor; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor. |

A substantial number of afferent neurons fail to respond to normal environmental stimuli.
BPH. In contrast, Reuther and colleagues\(^{44}\) found that elimination of detrusor instability in BPH patients after intravesical lidocaine was predictive of cure of symptoms after transurethral resection of the prostate. In rabbits with obstructed bladders, intravesical lidocaine but not anticholinergics, potassium channel openers, or calcium channel antagonists inhibited hyperreflexia.\(^{35}\) Lidocaine eliminates pain associated with intravesical capsaicin, indicating its ability to inhibit VR-1–expressing afferents found beneath the urothelium. In contrast, intravesical TTX fails to block intravesical capsaicin-induced abdominal licking (a behavioral manifestation of bladder pain) in rats, implying that VR-1–expressing bladder afferents are TTX-R.\(^{36}\) However, targeting Na\(^+\) channels expressed by suburothelial nerves may not be as effective as blocking those expressed by spinal nerves. Na\(^+\) channels may congregate at points of contact with second-order neurons in the spinal cord. Intrathecal lidocaine and especially bupivacaine eradicate urinary urgency and increase bladder capacity.\(^{77}\) These varied susceptibilities to Na\(^+\) blockade suggest that manipulation of Na\(^+\) channels expressed by spinal nerves or afferents could influence some disorders of micturition.

**Specific Conditions**

**Outlet Obstruction**

The development of a spinal micturition reflex with subsequent OAB occurs in other conditions besides SCI. Bladder outlet obstruction elicits enhancement of a spinal reflex.\(^{39}\) In humans with obstructed bladders, a capsaicin-sensitive spinal reflex can be detected using the ice-water test.\(^{29}\) Urethral obstruction stimulates increased expression of GAP-43, associated with axonal sprouting following injury (Figure 4).\(^{40}\) These observations imply de novo development of new spinal circuits following obstruction. Conversely, relief of obstruction is associated with the reduction of urinary frequency and reversal of these neural changes.\(^{40,41}\) This neuroplasticity persists in animals that fail to revert to normal voiding after relief of obstruction.\(^{41}\) Nevertheless, these findings are not mutually exclusive of changes in bladder smooth muscle that are also likely to participate in the development of OAB.\(^{42}\)

Bladder outlet obstruction initiates morphologic and electrophysiologic plasticity in afferents via NGF. NGF content is elevated in obstructed bladders in animals and humans, as well as in those with idiopathic instability.\(^{51,44}\) The increase in NGF content precedes the enlargement of bladder neurons and the development of urinary frequency.\(^{44}\) Moreover, blockade of NGF in obstructed animals using autoantibodies prevents neural plasticity and urinary frequency (Figure 5).\(^{44}\)

**Inflammation**

NGF has been shown to be increased in the bladders and urine of patients with IC and also in models of bladder inflammation in animals.\(^{46-47}\) Because NGF orchestrates events during the growth, maturation, and function of visceral afferents, one might anticipate that inflammation of the urinary bladder would be accompanied by neuroplasticity in sensory nerves. Repeated inflammatory stimuli elicit enlargement of bladder DRG neurons.\(^{46}\) Inflammation reduces the activation threshold for bladder afferents.\(^{46}\) Likewise, intravesical NGF lowers the threshold for bladder afferents. Plasticity within the spinal cord may also occur. Chemical or mechanical inflammation of the urinary bladder increases expression of the early-immediate gene C-fos within the lumbosacral spinal cord (Figure 4)\(^{50,52}\) in addition to overexpression of nitric oxide synthase in bladder DRG neurons.

Bladder overactivity induced by inflammation can be inhibited by a fusion protein that prevents interaction between NGF and its tyrosine kinase-A (trk-A) receptor (Figure 5).\(^{53}\) Hence, the neuroplasticity and the potential involvement of NGF in inflammatory conditions resemble those seen in obstruction.

**Spinal Cord Injury**

Insight into the mechanism underlying the increased mechanosensitivity of C-fibers after SCI has been gained by examining the DRG cells supplying the bladder. Plasticity in these afferents is manifested by enlargement of these cells\(^{54}\) and increased electrical excitability.\(^{77}\) A shift in expression of Na\(^+\) channels from a high-threshold TTX-resistant type to a low-threshold TTX-sensitive type occurs after SCI.

Plasticity in bladder afferents after SCI may involve the retrograde transport of substances from either the spinal cord or the bladder to the DRG neuron. Bladder DRG neurons are responsive to a variety of neurotrophins, especially NGF, which has been associated with hypertrophy of bladder DRG cells in a variety of conditions. Indeed, prevention of increased NGF levels in SCI rats prevents hyperreflexia. Alternatively, GDNF may be especially important because a small population of DRG neurons giving rise to C-fibers is nonresponsive to NGF but responds to GDNF.\(^{56}\) It is worth noting that other neurogenic disorders associated with urge incontinence respond to intravesical capsaicin therapy, suggesting that plasticity in C-fiber afferents could form the neurogenic basis for bladder overactivity.\(^{37,56,26}\) The emergence of a spinal reflex circuit activated by C-fiber bladder
affere...rhythm bladder contrac-

tions.69,70 Taken together, the pharma-
cologic data suggest that 5-HT acting

and its precursors, uptake blockers,
or 5-HT analogs inhibit bladder
activity in a variety of species.77 The
actions of 5-HT are complex and
mediated by over 13 different recep-
tors. Some data suggest that 5-HT
has a facilitating effect on voiding
via modulation of bladder afferents,
but intrathecal antagonists of 5-HT_2
and 5-HT_3 receptors reduce the vol-
ume threshold for voiding.68 The lat-
ter data suggest that descending 5-
HT pathways tonically depress blad-
der afferent input to the sacral spinal
cord. Moreover, the 5HT_2C agonists
MCPP and MK212 inhibit isovolu-
metric rhythmic bladder contrac-
tions.78,79 Taken together, the pharma-
cologic evidence indicates that some of the 13 receptors in the
CNS inhibits micturition reflex path-
ways. By analogy, a genomic pro-
clivity toward reduced 5-HT neuro-
transmission in the CNS may enhan-
ce bladder activity.

Because 5-HT influences both
emotional states and bladder func-
tion, are there shared conditions in
which this monoamine is altered? An
association between depression and
bladder complaints has been report-
ed. Zorn and colleagues71 studied 156
consecutive patients presenting to an
incontinence clinic and compared
their rates of depression to those of a
cohort of continent patients. Only
13% of patients with stress inconti-

ence or scored in the depressive
range on the BDI. In a cross-section-
al population-based study of 133
incontinent women, Melville and
colleagues72 found that nearly a
quarter of those with urge UI or
mixed UI had depression but only
2% of those with stress incontinence
did. These reports suggest that the
association of depression with mixed
or urge incontinence is significant,
but not that with stress urinary
incontinence. In the same study by
Melville and associates,72 nearly a
third of incontinent women had anx-
xiety or panic disorder, compared to
none of those with stress UI.

Animal models for depression and
anxiety demonstrate OAB. The spon-
taneously hypertensive rat (SHR) is a
useful animal model for studying
hypertension, anxiety, and attention
deficit disorder. SHRs void three times
as frequently as genetic controls.
Awake cystometrograms (CMGs) in
SHRs demonstrates unstable contrac-
tions. In humans, hypertension is
reputedly a risk for OAB due to
BPH.73 In addition, a significant
proportion of probands with the

 genetic polymorphism for anxiety
disorder have interstitial cystitis.74
Furthermore, many children with
attention deficit disorder exhibit
diurnal enuresis.75

5-HT can be depleted in the brain
by neonatal treatment with clomipramine.
Several months after this
treatment, rats demonstrate
behavioral responses consistent with
depression. These animals also void
more frequently and have more
unstable contractions than controls
do. In the clomipramine-treated and
SHR models of depression and anxiety,
respectively, reduced levels of 5-HT
in the brain are associated with low-
erd volume thresholds for voiding,
with unstable bladder contractions.
Interestingly, OAB persists in females
but not in males following puberty
in clomipramine-treated animals.
These data support a link among
altered 5-HT, emotional disorders,
and OAB.
Gender

Recent reviews suggest that OAB and urge incontinence are more common in women than in men and that both conditions are more prevalent at times of changing hormonal levels in women. Hormonally induced differences in neurotransmitter systems (eg, by 5-HT) may explain this sexual difference in OAB in the nonelderly. Genetic, psychosocial and biologic factors seem to account for this sexual dichotomy. Estrogen and progesterone appear to influence bladder contractions and voiding frequency. Female hormones may also influence nerves. One target of estrogens in the CNS may be 5-HT neurons. This could again link 5-HT, emotional disorders, and OAB in the context of differences between men and women. The serotonergic system plays a major role in depression, although there are other neurotransmitters involved. Differences in 5-HT function may explain why depression is more common in women. Women may be pre-disposed to both OAB and depression in part because levels of 5-HT in the brain are substantially lower in women than in men. When rates of 5-HT synthesis were measured in the human brain using PET, the mean rate of synthesis in normal males was found to be 52% higher than in normal females.

By virtue of reduced 5-HT in the CNS, there may be fewer inhibitory mechanisms for autonomic events such as voiding. This could result in some women in a predisposition to OAB, depression, anxiety, eating disorders, and chronic pain states such as IC, fibromyalgia, and irritable bowel syndrome. The model is too simplistic to provide a universal explanation for all instances of OAB, but the pharmacogenomic basis for these shared traits merits further study.

Conclusion

Alterations in smooth muscle excitability and changes in bladder innervation orchestrated by neurotrophins manufactured by the detrusor are temporally linked with OAB. Direct proof in humans is difficult to obtain, but circumstantial evidence is compelling. The ability of local anesthetics, intravesical afferent neurotoxins, and destruction of afferent nerves in the bladder neck and prostate to reduce urgency, frequency, and urge incontinence indicates an important role for afferent evoked reflexes. The detection of a spinal reflex (positive ice-water test) in patients with neurogenic bladders and obstruction suggests a shared underlying plasticity in nerves supplying the bladder. The molecular basis for this plasticity may be a channelopathy. In addition, genetic or hormonally induced discrepancies may explain the preponderance of OAB and urge UI in middle-aged women and in certain men. The realization that OAB may arise from nerves supplying the smooth muscle with a proclivity toward increased coupling with the detrusor or from altered urothelial function with disease offers an avenue for therapeutic intervention.

References

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Main Points

• There is evidence that overactive bladder (OAB) of different etiology has common causative mechanisms.
• Changes in the macroscopic structure of unstable bladder include muscle bundle denervation and smooth muscle cell hypertrophy; ultrastructural changes like protrusion junctions and unusually close abutments between the myocytes are common.
• Local anesthetics, intravesical afferent neurotoxins, and destruction of afferent nerves in the bladder neck and prostate reduce urgency, frequency, and urge incontinence, indicating an important role for afferent evoked reflexes.
• High excitability and connectivity of smooth muscle in the unstable bladder allow propagation of electrical activity that could cause an uninhibited contraction.
• Neuroplastic changes associated with OAB may result from alterations in activity in the nerves controlling the detrusor and probably involve nerve growth factor.
• OAB often occurs after spinal cord injury or bladder obstruction or inflammation, which may trigger neuroplasticity.
• People with depression, anxiety, attention deficit disorder, and other conditions associated with disturbed serotonin metabolism may be predisposed to OAB.


