New Frontiers in the Treatment of Overactive Bladder

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INTRODUCTION

Overactive bladder (OAB) is a term used to describe symptoms of urinary frequency, urgency with or without urge incontinence (1). Because the patients with OAB are often reluctant to seek medical help, the actual incidence is difficult to be assessed. The OAB is generally more common in women than in men and estimated to affect between 50 and 100 million people worldwide (2). Traditional anticholinergic drugs are the “gold standard” for treating the OAB today. Tremendous advances over the past few years, especially with advanced drug delivery systems, have improved efficacy and decreased side effects when treating OAB. However, most urologists would readily acknowledge that when it comes to treating our patients with OAB, we still have a long way to go in finding drugs that can further improve efficacy and decrease the incidence and severity of side effects (3). The basic science associated with voiding function is on the way of its development to understand pathophysiology underlying OAB. In this article we try to forecast how urologists will treat the OAB and associated urinary incontinence in the next decade based on recent advances in research field of neurourology.

Key Words: Overactive bladder, Incontinence, Treatment, Duloxetine

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1. Transdermal oxybutynin

We are excited about the prospect of transcutaneous anticholinergic drug delivery. It is logical that transcutaneous application of anticholinergic drugs can further decrease side effects while still maintaining efficacy. Transdermal delivery of oxybutynin decreases first-pass drug metabolism in the liver and gut wall and allows a lower concentration of oxybutynin metabolites. The metabolites of oxybutynin, rather than the parent component itself, appear to account for the majority of the dry mouth side effects (4). If once- or twice-a-week transcutaneous anticholinergic patches can be developed, then higher-dose regimens as well as increased patient compliance can be expected.

Davila and colleagues recently reported on the outcome of a multicenter, randomized, double-blind study of transdermal versus immediate-release oral oxybutynin (5). Transdermal oxybutynin achieved reductions in urge incontinence episodes similar to those seen with oral immediate-release oxybutynin but with significantly less occurrence of dry mouth.

2. Bladder-specific anticholinergics

Pharmacologically defined subtype-selective drugs have been developed. Darifenacin and vamicamide have recently been demonstrated to be selective for the M$_3$ receptor subtype. Darifenacin, which has 11 times the affinity for M$_3$ that it has for M$_2$ receptors, was similar in potency to atropine in blocking acetylcholine (ACh)-induced contractions of the guinea pig urinary bladder but had one-fifth the affinity of atropine for M$_3$ receptors in the parotid gland (6). Similarly, in the anesthetized dog, darifenacin was 8.6 times as potent in blocking pelvic nerve-evoked bladder contractions as in suppressing trigeminal nerve-evoked salivation (7). Thus, darifenacin is a highly promising M$_3$ subtype-affinity agent under investigation for OAB. If the phase 3 studies confirmed the pharmacologic advances, darifenacin would be an attractive agent.

(S)-Oxybutynin is a single-isomer version of racemic oxybutynin. Racemic oxybutynin exhibits two pharmacologies, one related to relaxation of the bladder’s detrusor muscle and the second related to anticholinergic activity. (S)-oxybutynin may possess a superior balance between bladder relaxation and anticholinergic activity. In a phase IIB, 12-week study in over 650 patients, (S)-oxybutynin, at 120 mg three times a day, demonstrated a statistically significant improvement in the reduction of combined micturitions, voluntary micturitions, and number of patients achieving complete continence compared with placebo.

3. Antidiuretic hormones

Desmopressin is a synthetic vasopressin analog with strong antidiuretic effects. The drug is commonly used in children with nocturnal enuresis. The use of desmopressin at bedtime for bothersome nocturia is becoming more popular nowadays. The initial reports in patients with neurogenic bladder dysfunction were encouraging (8). More recently, desmopressin is being considered for treatment of nocturia associated with benign prostatic hypertrophy (BPH) and OAB. Cautions must be practiced before considering desmopressin in any patient with cardiovascular risk factors, including angina and congestive heart failure. Dilutional hyponatremia can occur very quickly and pose a health risk to these patients.

4. Modulation of the micturition and continence reflexes

Selective serotonin and norepinephrine reuptake inhibitors, like duloxetine, that are specific for reflexes that control the bladder and urethra have the promise for treating not only OAB but also stress incontinence (9). At present, there are no clinically proven pharmacotherapies acting in the central nervous system to treat OAB. However, recent advances in animal studies have revealed potential targets in the brain and spinal cord for the treatment of OAB.

The sympathetic and parasympathetic autonomic nuclei as well as the sphincter motor nuclei receive a prominent serotonergic input from the raphe nuclei in the caudal brain stem. Activity in the serotonergic pathway generally enhances urine storage by facilitating the vesicosym pathetic reflex pathway and inhibiting the parasympathetic micturition pathway (10,11). Among the various subtypes of 5-hydroxytryptamine (5-HT) receptors, 5-HT$_2$ and 5-HT$_3$ receptors mediate excitatory effects on sympathetic and somatic reflexes to increase outlet resistance, whereas 5-HT$_2$c and 5-HT$_3$ receptors are involved
in inhibition of the micturition reflex. Targeting specific subtypes of 5-HT receptors could offer new treatments for lower urinary tract dysfunctions such as OAB or stress incontinence. For example, duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is most promising presently, and is now in U.S. Food and Drug Administration clinical trials for both urge and stress incontinence. In animal models, duloxetine has been shown to significantly increase bladder capacity and sphincter tone without interfering with the normal micturition cycle (11).

5. Bladder peppers

Capsaicin and resiniferatoxin (RTX) are drugs derived from plants in the pepper family, commonly referred to as the vanilloids. Capsaicin and RTX activate nociceptive sensory nerve fibers through an ion channel known as vanilloid receptor subtype 1 (VR1) (12). This receptor is a nonselective cation channel and is activated by heat and protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity in vivo. Vanilloid receptors are located predominantly on C-fiber bladder afferents, and activation of the receptors initially excites and subsequently desensitizes C fibers.

The bladder afferent pathways consist of myelinated A-delta fibers and unmyelinated C fibers. A-delta fibers transmit signals from mechanoreceptors that initiate the normal micturition reflex, while C-fiber bladder afferent signals are not essential for normal voluntary voiding. However, various pathologic conditions, such as spinal cord injury or chronic bladder irritation, induce sensitization and/or recruitment of C fibers, resulting in an overall increase in the C-fiber contribution to mechanotransduction and bladder overactivity.

RTX is a much more potent sensory antagonist than capsaicin. It is approximately 1,000 times “hotter” than capsaicin. Like capsaicin, it possesses vanilloid receptor agonist activity, resulting in desensitization. The key advantage of RTX is that it is at least as effective as capsaicin, without many of the local side effects, such as pain and inflammatory peptide release. Recently, there are reports of RTX’s being effective for the treatment of nonneurogenic urge incontinence, OAB, and even interstitial cystitis (12).

6. Poisoning the OAB

Botulinum toxin, first isolated by Emile van Ermengem in 1897, is the most potent biological toxin ever known. A single gram of this toxin, if maximally distributed, can kill 1 million people! The toxin acts by inhibiting ACh release at the presynaptic cholinergic junction. Inhibition of ACh release results in regionally decreased muscle contractility and muscle atrophy at the site of injection. The chemical denervation that results is a reversible process, as axons resprout in approximately 3 to 6 months (13) (Figure 1).

Urologically, botulinum toxin has been used to treat spinal cord-injured patients who suffer from detrusor-external sphincter dyssynergia (14). More recently, Schurch and colleagues reported successful treatment of spinal cord-injured patients with detrusor hyperreflexia using intravesical botulinum toxin injections at up to 30 sites (15). The authors demonstrated a significant increase in mean maximum bladder capacity (from 296 mL to 480 mL, P < 0.016). The clinical effects begin within 5 to 7 days and last up to 6 months.

Recent animal research demonstrated marked decreases in the release of labeled norepinephrine and ACh in botulinum-injected rat bladder and urethra (13). While the therapeutic effect of inhibiting ACh release is obvious, blockage of norepinephrine release may also provide clinical benefit by inhibiting sympathetic transmission and smooth-muscle dysynergia. The potential treatment targets of botulinum would
therefore include not only detrusor-external sphincter dyssynergia but also BPH and OAB. Phelan and coworkers have expanded the role of urethral injections to include treatment for women patients: those with urinary retention after pubovaginal sling placement or secondary to pelvic floor spasticity and those with acontractile bladder who wish to void by means of the Valsalva maneuver (16). With injection localized to the external sphincter, the risk of developing stress urinary incontinence has been minimal in our personal experience over the past 3 years.

### Potential Therapies by 2010

1. **Potassium channel openers**

One promising class of drugs that a number of pharmaceutical companies are considering for the treatment of OAB is potassium channel openers (KCOs). Drugs, such as cromakalim, pinacidil, and ZD6169, that open ATP-sensitive K+ (KATP) channels and produce membrane hyperpolarization are effective in suppressing spontaneous action potentials and isolated contractions of bladder smooth muscle. KATP channel openers are less effective in blocking neurally evoked than spontaneous bladder contractions and therefore should be more active in suppressing unstable bladder contractions during bladder filling and not interfere with normal voiding. Oral administration of ZD6169 reduces voiding frequency in rats and dogs without lowering blood pressure (17). Intravesical administration in rats increases the bladder volume for inducing a micturition reflex and also decreases the frequency and amplitude of spontaneous bladder contractions and reduces voiding pressure in both normal and outlet-obstructed animals (17,18). It has been suggested that the drug acts not only on bladder smooth muscle but also on capsaicin-sensitive bladder afferents to reduce afferent firing induced by bladder distention or chemical irritation of the mucosa (18).

2. **Tachykinin antagonists and afferent peptides**

Tachykinins released in the bladder can act on: 1) NK-1 receptors in blood vessels to induce plasma extravasation and vasoconstriction; 2) NK-2 receptors to stimulate the bladder contractions; and 3) NK-2 receptors on primary afferent terminals to increase excitability during bladder filling or during bladder inflammation (18). Substance P also acts on receptors on urothelial cells to release nitric oxide (NO). Intrathecal administration of NK-1 antagonists increased bladder capacity in normal conscious rats without changing voiding pressure, whereas NK-2 antagonists were ineffective. Bladder hyperactivity in rats was also suppressed by intrathecal injection of NK-1 antagonists. Bladder hyperactivity induced by capsaicin was reduced by an NK-2 antagonist (SR 48,965) that did not influence normal voiding (19). TAK-637, which is a highly specific antagonist for the NK-1 receptor, is also reportedly effective to suppress bladder activity in guinea pigs (20). The key advantage of tachykinin antagonists is that there is essentially no decrease in detrusor contractility and no increase in residual urine or retention risk. The drug works on the sensory nerves innervating the bladder and not on the bladder itself. Would it not be lovely to have one drug that can help not OAB, irritable symptoms of BPH, and interstitial cystitis and yet causes no dry mouth or risk of urinary retention?

3. **Detrusor specific β3-adrenergic receptor agonists**

A fascinating and promising new approach for the treatment of the OAB that the general urology community may not be familiar with is use of β3-adrenergic receptor agonists. Recent studies have demonstrated that the predominant bladder β3-adrenergic receptor subtype in humans is the β3-receptor. Thus, selective activation of β3-adrenergic receptors could be useful for treating OAB by directly relaxing human bladder smooth muscle with, we hope, minimal systemic side effects (21).

4. **Advanced drug delivery**

Intravesical instillation of oxybutynin has been demonstrated to have efficacy in patients with OAB in whom oral oxybutynin failed, proved subtherapeutic, or was not tolerated. Let’s consider an apparent oxybutynin paradox: Why can higher concentrations of oxybutynin be delivered via intravesical instillation, dermal patch, or oral controlled-release technology with less side effects than oral immediate-release oxybutynin?

The key is that dry mouth, due to anticholinergic effects on the salivary gland, is produced to a much greater extent by oxybutynin’s metabolite, desethyloxybutynin, than by the parent compound itself. Desethylxybutynin is produced not only by
first-pass metabolism in the liver but also by direct cytochrome P450 metabolism in the proximal gut wall (stomach and duodenum) (5).

Where oxybutynin is delivered can alter the amount of metabolites that enters the systemic circulation. Intravesical delivery of oxybutynin should yield significantly less metabolite formation. If constant therapeutic levels of oxybutynin in the bladder can be achieved without repeated instrumentation, this would provide an extremely effective regimen for controlling OAB. The key to this intravesical regimen is a long-lasting intravesical pump to deliver the desired dose of drugs. This technology is not available today but is currently under development (22).

5. Purines

Contractions of normal human bladder are induced primarily by ACh released from cholinergic nerve terminals in the bladder. It has been reported that nonadrenergic, noncholinergic bladder contractions are induced by increases of ATP levels in the human bladder under pathologic conditions such as de-nervation, bladder outlet obstruction, or idiopathic urge incontinence (23).

ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G protein-coupled receptor family (P2Y). P2X1 receptors have also been detected in the wall of the bladder in a suburothelial plexus of afferent nerves. In P2X1 knockout mice, afferent activity induced by bladder distention was significantly reduced (24).

In patients with idiopathic detrusor instability, numbers of detrusor P2X2 receptors were significantly elevated, whereas those of other P2X receptor subtypes were significantly decreased (23). There was no detectable purinergic component of nerve-mediated detrusor muscle contractility in normal women without instability. However, there was a significant (approximately 80%) purinergic contractility component in bladder of women with detrusor instability.

In conclusion, the purinergic pathway may be a novel target for the pharmacological treatment of OAB. P2X-receptor acting agents could modulate efferent/afferent activities to treat OAB if receptor subtype-specific agents become available.

6. Bladder-selective PDE inhibitors

Phosphodiesterase (PDE) is the enzyme that catalyzes the degradation of cyclic adenosine monophosphate (cAMP) to AMP and thus limits the action of cAMP. There are several classes of PDEs that have individual substrate affinities, specific species and tissue distributions, and pharmacologic selectivities (25). Considerable research is currently under way to try to identify the specific isoform of PDE present in the bladder as opposed to that in the penis. Selective inhibition of bladder PDE would result in both an increase in the basal levels of cAMP (and possibly relaxation of the detrusor) and enhancement of the sensitivity and efficacy of β-adrenergic receptor agonists. Thus, a selective β-adrenergic receptor agonist or a selective PDE inhibitor might prove effective alone or in combination for relaxation of the detrusor.

Star Trek Urology: To Boldly Go Where No Urologists Have Gone Before

1. Pharmacogenomic medicine

Through microarray gene chip technology, we can determine a patient’s drug metabolism profile, receptor profile, and allergy risk. These factors can be used to screen a list of medications prior to therapy. A urologist will then always be able to choose the best drug for each patient every time without the risk of allergic reaction.

2. Gene therapy

The bladder is ideally suited for molecular medicine. Through gene therapy we can replace, supplement, or suppress a protein or cytokine to correct a disease process. I would like to give three examples.

First, let’s consider gene therapy for the treatment of OAB. Large-conductance calcium-sensitive (KCa, or maxi-K) channels play a role in modulating contraction and relaxation responses in smooth muscle cells. Bladder injection of low-efficiency gene transfer of the hSlo/pDNA3 (the pore-forming subunit of the human maxi-K channel) blocked detrusor hyperactivity in partially urethral-obstructed female rats (26). It is hypothesized that expression of hSlo in rat bladder functionally antagonizes the increased contractility normally
observed in obstructed animals and thereby ameliorates bladder overactivity.

Second, I believe that there may be a way to prevent the inevitable deteriorations of diabetic neurogenic bladder through organ-specific gene therapy. In a rat model of diabetic cystopathy, the bladder wall is injected with a specially constructed nonreplicating human herpes simplex virus (HSV) vector. This recombinant herpes vector mediates expression of \( \beta \)-nerve growth factor (\( \beta \)-NGF), a neurotrophic factor that in experimental conditions has been shown to prevent and reverse diabetic neuropathy. Using the safe, nonreplicating, latent HSV vector, expression of \( \beta \)-NGF occurs not only in the bladder but also in the dorsal root ganglion of the pelvic nerve. We have exciting data suggesting that overexpression of \( \beta \)-NGF in the bladder and dorsal root ganglia can decrease diabetic cystopathy (27).

Third, what about the single condition most troubling to just about every urologist, interstitial cystitis (IC)? Can the introduction of a viral vector that is targeted to nerves and that carries a gene for an endogenous opioid peptide, which blocks pain pathways, be used to help alleviate pain, regardless of the cause of IC? HSV vector-mediated gene can be transferred to the bladder and bladder afferent nerves of preproenkephalin (PPE), a precursor of enkephalin, which was initially designed for the treatment of bladder pain (Figure 2). Since opioid peptides such as enkephalin are known to suppress not only pain but also the micturition reflex, HSV-PPE gene therapy can be a potential modality for treating OAB as well as bladder pain (28).

### 3. Stem cell tissue engineering

Can we use tissue engineering and stem cell technology to actually rebuild the damaged bladder and urethra? Because the bladder and urethral smooth muscle generally lack regenerative ability, research has centered on tissue repair by using pluripotent stem cells derived from other lineages (29,30). Through purifying techniques, muscle-derived stem cells that can differentiate into urinary tract smooth muscle and improve the function of the bladder wall and urethral sphincter may become possible.

Stem cell-based tissue engineering can also be a platform for ex-vivo gene therapy. The aim of ex-vivo cell therapy is to replace, repair, or enhance the biological function of damaged tissues or organs. An ex-vivo process involves harvesting of cells from patients or donors, in-vitro manipulation to enhance the therapeutic potential of the harvested cells (ex-vivo gene therapy), and subsequent injection or implantation of the cells into the patient. One particular advantage of cell-based ex-vivo gene therapy is that the manufactured cells act like bioreactors (31). At any stage of the process, cells can be cryopreserved so that therapy can be scheduled according to the patient’s requirements.

### CONCLUSIONS

The OAB is a rising clinical problem, which provides a considerable challenge for the urologists. We believe that there is great hope for future translational research on voiding dysfunction and urinary incontinence. We believe that the key to the next major advance is to focus on afferent nerve intervention to prevent OAB. Afferent blockade, a revised treatment approach, targets the afferent nerves that control the bladder. Wouldn’t it be more desirable to prevent urgency and the micturition reflex that initiates OAB? There are a number of afferent blockade drugs now in development that can prevent the bladder from having this involuntary contraction. Treating
the patient with OAB using this approach would allow the possibility of giving lower drug doses with fewer side effects, as well as greater efficacy. Drugs that work on the unmyelinated C-fiber afferent limb of the micturition reflex do not present the risk of urinary retention that occurs with the use of anticholinergic drugs. Studies are also under way of advanced drug delivery systems, gene therapy, and tissue engineering as potential therapies further into the future. All of these efforts would provide an effective therapy with little unwanted effects for OAB and urinary incontinence in the next decade.

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