Novel Treatment of Overactive Bladder and Detrusor Overactivity with Intravesical Resiniferatoxin

Hann-Chorng Kuo, M.D.

Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan

THE UROTHELIUM AND OVERACTIVE BLADDER

The urothelium has been shown to be a responsive structure for both sensor (ability to respond to thermal, mechanical and chemical stimuli) and transducer (ability to release chemicals) functions. The afferent nerves and urothelial cells in the bladder have common properties including the expression of certain receptors and ion channels (such as transient receptor potential vanilloid receptor 1, TRPV-1), the purinergic receptor $P2X_3$, and the sensory neuropeptides substance P and calcitonin gene-related peptide (CGRP) [1-3]. Patients with neurogenic detrusor overactivity (NDO) due to spinal cord lesions were found to have increased TRPV-1 and $P2X_3$ expression in suburothelial innervation [4]. Women with idiopathic detrusor overactivity (IDO) were found to have increased density of suburothelial substance P and CGRP immunoreactive fibers compared to controls [3].

The actual pathophysiology of detrusor overactivity (DO) after neurogenic lesions, bladder outlet obstruction (BOO) and ageing has not been well explored. The $P2X_3$ receptors are co-localized with TRPV-1 receptors and are believed to be involved in afferent pathways that control urinary bladder volume reflexes [5]. Increased stretch activated adenosine triphosphate (ATP) release has been reported from human urothelial cells cultured from the bladders of patients with interstitial cystitis and spinal cord injury.

ROLE OF C FIBERS IN OVERACTIVE BLADDER

In the mammalian bladder, unmyelinated sensory afferent C-fibers have been found to become predominant and mediate the detrusor reflex after spinal cord transection [6]. Intravesical vanilloid therapy using capsaicin or resiniferatoxin has been found to act on the vanilloid receptors VR-1 (TRPV-1) and is an effective therapy in patients with detrusor hyperreflexia due to spinal cord lesions [7]. Vanilloid receptors VR-1 are found on the afferent nerves in the lamina propria and co-localize with acetylcholine- containing nerve fibers as well as substance P and CGRP in rat bladders [8-10]. Moreover, many C fibers in the bladder mucosa contain sensory neuropeptides (such as substance P, neurokinin A, CGRP) which on release, can modulate the micturition reflex and might cause detrusor overactivity [11]. A local inflammatory process might be induced through the afferent and efferent nerves in these interstitial cellular networks which integrate signal transmission from the urothelium to detrusor muscles in the bladder wall [12].

Based on results from recent investigations, bladder disorders such as NDO, IDO, interstitial cystitis (IC), overactive bladder (OAB) due to BOO and urothelial dysfunction might have a common pathway in abnormality of expression of sensory receptors or release of transmitters in the suburothelial nerves or interstitial cells [12]. In this regard, inhibition of receptor expression or transmitter release in the sensory nerve terminals in the suburothelial space might have good therapeutic effects in treatment of sensory urgency, IC and DO.

Received: January 29, 2007 Accepted: February 28, 2007
Address correspondence to: Dr. Hann-Chorng Kuo, Department of Urology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung Yang Road, Hualien, Taiwan
E-mail:hck@tzuchi.com.tw

CURRENT TREATMENT OF OAB

OAB is a symptom syndrome characterized by urgency frequency with or without urge incontinence that may affect patients' quality of life [13]. OAB is diagnosed by subjective symptoms, of which the core symptom is urgency. Both sensory urgency and DO might be involved in the pathophysiology of this symptom syndrome. This condition may wax and wane and occasionally associates with symptoms of suprapubic pain at full bladder. Current treatments are usually unsuccessful in completely eradicating the urgency sensation. Behavioral therapy or pelvic floor muscle training have been tried to relieve this bothersome syndrome [14]. Some patients with OAB and hypersensitive bladder may respond to antimuscarinic agents [15]. However, this treatment has some adverse effects such as dizziness, dry mouth, blurred vision, and constipation, which some elderly patients are unable to tolerate [16]. Intradetrusor botulinum A toxin injection has been tried and satisfactory results have been achieved in increasing bladder capacity and decreasing the urgency sensation in patients with NDO and IDO [17,18]. However, increased postvoid residual volume and urinary retention, which can develop in the first post-treatment month, may prohibit its wide-spread application in the patients with mild to moderate symptoms refractory to antimuscarinic agents [19]. Therefore, it is mandatory to search for an effective alternative therapy that does not have serious adverse effects that can be applied to patients with OAB.

There is not yet a conclusion on the pathophysiology of hypersensitive and OAB. Although urothelial dysfunction and changes in the urinary potassium concentration have been proposed to account for this condition, treatments aimed at these pathophysiologies have not been able to alleviate this condition adequately [20,21]. It is also possible that the chronic symptomatology in bladder hypersensitivity is due to central sensitization and persisting abnormality or activation of the afferent sensory system [22]. Intradetrusor injection of botulinum A toxin has been found to modulate the release of neurotransmitters from sensory nerve endings, and effectively modulate the inflammatory process mediated by nociceptive afferent nerve dysfunction [23,24].

RESINIFERATOXIN

Resiniferatoxin is a capsaicin analog that is specific for the vanilloid receptors in the bladder. It was recently demonstrated that vanilloid receptors are present not only on sensory fibers but also in bladder urothelium and smooth muscle cells [25-27]. Recent study has demonstrated that vanilloid receptors TRPV1 participate in normal bladder function, are essential for normal mechanically evoked purinergic signaling by the urothelium and are involved in ATP release [28]. In NDO and IDO, there is up-regulation of unmyelinated nerve fibers expressing vanilloid receptors [1]. The vanilloid receptors on the sensory fibers in the bladder become overexpressed in DO, and this is the key for successful treatment with resiniferatoxin. In patients with spinal cord injury, vanilloid-sensitive fibers in the bladder assume a central role in the reflex emptying of the bladder at low volumes [29]. Instillation of resiniferatoxin can desensitize vanilloid receptors on the sensitive fibers resulting in the disappearance of spontaneous detrusor contractions during bladder filling [30].

MECHANISM FOR RESINIFERATOXIN ON DETRUSOR OVERACTIVITY

Purinergic $P2X_3$-immunoreactive nerve fibers in NDO were found to decrease in the patients who responded to intravesical resiniferatoxin [31]. Previous study showed that instillation of 50 nM resiniferatoxin can delay or suppress involuntary detrusor contractions during filling cystometry, hence, explaining the mechanism by which urinary incontinence can disappear or improve after resiniferatoxin treatment [32]. This finding indicates that vanilloid-sensitive fiber input has an important role in the generation of involuntary detrusor contractions in patients with NDO and IDO [33]. Although intravesical resiniferatoxin treatment is theoretically effective in the treatment of DO, successful therapeutic results are not obtained in many patients. The success rate (including continence rate and improvement rate) in recent studies using a single instillation of resiniferatoxin at concentrations of 50 nM to 100 nM was reported to be about 50% or less [34]. Recent studies have demonstrated that the therapeutic effect of multiple low dose resiniferatoxin was significantly superior to a placebo, indicating that desensitization of vanilloid receptors in the bladder can reduce DO and improve urinary incontinence [35,36].

INTRAVESICAL RESINIFERATOXIN THERAPY

Previous investigations in intravesical vanilloid therapy were aimed at treating NDO due to spinal cord lesions [7,37,38]. Only a few investigations have used capsaicin or resiniferatoxin to treat DO or bladder hypersensitivity in non-spinal cord lesions [30,39]. As evidenced by positive ice water test results, overexpression and hyperactivity of the vanilloid receptors of the urinary bladder have been identified in patients with DO due to various non-spinal lesions [40]. Therefore, use of intravesical vanilloid agonists such as capsaicin or resiniferatoxin to treat DO refractory to anticholinergic agents might be effective.

Intravesical capsaicin therapy exerts an excellent effect in patients with incontinence due to multiple sclerosis or spinal cord injuries [41-43]. However, due to its irritative effect, patients with non-spinal lesions might not be able to tolerate capsaicin therapy. Resiniferatoxin, an ultrapotent capsaicin analog, has been shown to have a clinical effect similar to capsaicin but with less neuronal excitation [44]. Thus, resiniferatoxin treatment is more suitable than capsaicin for patients who have normal bladder sensation and OAB [45].

Resiniferatoxin treatment has been demonstrated to have a therapeutic effect in patients with detrusor hyperreflexia due to spinal cord lesions [33,46,47]. At a concentration of 100 nM resiniferatoxin can induce full desensitization and successfully treat detrusor hyperreflexia in neurologically impaired patients who do not improve after capsaicin treatment [33]. In one study, a 50 nM solution of resiniferatoxin was found to delay or suppress involuntary detrusor contractions during filling cystometry in patients with IDO [30]. These findings indicate that desensitization of capsaicin sensitive primary afferents by intravesical resiniferatoxin can have a therapeutic effect in hyperactive or sensory disorders of the urinary bladder.

The clinical effect of intravesical resiniferatoxin at a concentration of 100 nM has been demonstrated in treating DO due to non-spinal cord lesions in patients refractory to anticholinergic treatment [35]. Twenty-one of 41 patients with NDO and urinary incontinence had clinical improvement (51.2%) whereas 18 had a stationary result and 2 developed urinary retention with overflow incontinence. The effects of resiniferatoxin treatment in these 21 patients lasted for 2 to 9 months with a median duration of 5 months. After treatment, the cystometric capacity significantly increased, and detrusor pressure showed a significant reduction, but the maximal flow rate and residual urine volume showed no significant difference. Among the 20 patients who failed treatment, only 4 (20%) had an increase in maximal cystometric capacity by 50% and none had a reduction in detrusor pressure.

The magnitude of the neurotoxic effect of resiniferatoxin seems to depend on the dose of vanilloids that is administered. The dose that we used in one study may have had temporary neurotoxcity but was insufficient to cause any irreversible effects. Nevertheless, a reduction in detrusor pressure might account for the decrease in urgency and urge incontinence in patients with DO. The causes for failed treatment with resiniferatoxin have not been elucidated. If complete desensitization of vanilloid receptors accounts for a successful result, then repeat treatment with resiniferatoxin may be helpful in complete blockage of vanilloid receptors. A high concentration of resiniferatoxin might cause acute desensitization but might also result in neurotoxicity to the A-delta fibers mediating detrusor contractions, whereas a lower concentration might have less neurotoxicity and less desensitization of C-fibers. In order to achieve better desensitization of C-fibers without neurotoxicity to A-delta fibers, repeat treatment with a lower concentration of resiniferatoxin might be necessary.

LOW DOSE MULTIPLE RESINIFERATOXIN INSTILLATIONS

In order to obtain a better therapeutic outcome, the concentration of resiniferatoxin and the treatment regimen were changed to four instillations utilizing a solution of 10 nM resiniferatoxin for adequate desensitization of vanilloid receptors. The results from a recent randomized, double-blind, placebo-controlled study have shown that multiple resiniferatoxin instillations at a concentration of 10 nM is well tolerated and effective in about 50% of patients with refractory detrusor overactivity compared to the control group 3 months after instillation [36]. Although the adverse effects after this treatment were minimal, the therapeutic effect decayed with time and only 34.6% of the patients exhibited a successful result at 6 months [36].

Fifty seven patients completed the trial and were included in the final analysis. There were 34 men and 23 women who completed all

four treatments (90%). At 1 month, the success rate in the resiniferatoxin group was significantly better than in the control group (78% vs 24%, p<0.001). At 3 months after treatment, the success rate remained significantly higher in the study group compared to the control group (50% vs 14%, p<0.001). At 6 months after treatment, the treatment remained effective in 28.6% of patients in the study group, but only 3.5% of the control group (p<0.001). At 12 months, the treatment remained effective in only 3 patients (11%) in the study group and none in the placebo group (p<0.001). The results of this phase II study showed that multiple intravesical instillations of 10 nM resiniferatoxin had a significantly superior therapeutic outcome compared with a placebo in patients with refractory DO. The therapeutic results obtained with multiple instillations of 10 nM resiniferatoxin at 3 months in this study were similar to those in another study [35].

The success rate with multiple intravesical instillations of resiniferatoxin at a concentration of 10 nM is higher than that using a single instillation of resiniferatoxin at a concentration of 50 or 100 nM [30,34], suggesting that a single intravesical instillation of 50 or 100 nM resiniferatoxin might not achieve adequate desensitization. In previous double-blind, placebo-controlled trials of intravesical resiniferatoxin for spinal detrusor overactivity, the effects of resiniferatoxin in increasing bladder capacity were controversial [32, 34]. The therapeutic effect of a single instillation of resiniferatoxin might be affected by several factors, such as urine dilution during treatment, and reflexic expulsion of the instilled solution. These factors may result in unknown actual concentrations in the bladder and could result in diverse therapeutic results [34]. Repeated instillations might lead to greater desensitization of afferent fibers and can provide a satisfactory therapeutic outcome in the majority of patients [35,36].

REFERENCES

1. Brady CM, Apostolidis AN, Harper M, et al: Parallel changes in bladder suburothelial vanilloid receptor TRPV1 (VR1) and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical resiniferatoxin treatment. BJU Int 2004; **93**:770-776.
2. Brady C, Apostolidis A, Yiangou Y, et al: P2X3-immunoreactive nerve fibers in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin (RTX). Eur Urol 2004; **46**:247-253.
3. Smet PJ, Moore KH, Jonavicius J: Distribution and colocalization of calcitonin gene-related peptide, tachykinins, and vasoactive intestinal peptide in normal and indiopathic unstable human urinary bladder. Lab Invest 1997; **77**:37-49.
4. Apostolidis A, Popat R, Yiangou Y, et al: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of Botulinum toxin for human detrusor overactivity. J Urol 2005; **174**;977-983.
5. Cruz F, Avelino A, Cruz C, et al: Sensory fibers immunoreactive to the vanilloid receptor protein: Distribution in the urinary bladder. Neurourol Urodynam 2000; **19**:456.
6. De Groat WD: A neurological basis for the overactive bladder. Urology 1997; **50(Suppl 6A)**:36.
7. Fowler CJ, Beck RO, Gerrard S, et al: Intravesical capsaicin for treatment of detrusor hyperreflexia. J Neurol Neurosurg Psych 1994; **57**:169.
8. Wiseman OJ, Fowler CJ, Landon DN: The role of the human bladder lamina propria myofibroblasts. BJu Int 2003; **91**:89-93.
9. Avelino A, Cruz C, Nagy I, Cruz F: Vanilloid receptor 1 expression in the rat urinary tract. Neuroscience 2002; **109**:787-798.
10. Yiangou Y, Facer P, Ford A, et al: Capsaicin receptor VR1 and ATP-gated ion channel P2X3 in human urinary bladder. BJU Int 2001; **87**:774-779.
11. Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP: Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int 2004; **45**:987-993.
12. Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006; **49**:644-650.
13. Abrams P, Kelleher CJ, Kerr LA, Rogers RG: Overactive bladder significantly affects quality of life. Am J Manag Care 2000; **6(Suppl 11)**:S580-590.
14. Ouslander JG: Mangement of overactive bladder. N Eng J Med 2004; **350**:786-799.
15. Chapple CR: Muscarinic receptor antagonist in the treatment of overactive bladder. Urology 2000; **55(5A Suppl)**:33-46.
16. Yarker Y, Goa KL, Fitton A: Oxybutynin: A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging 1995; **6**:243.
17. Reitz A, Stohrer M, Kramer G, et al: European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004; **45**:510-515.
18. Kuo HC: Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. Urology 2004; **63**:868-872.
19. Kuo HC: Clinical effects of suburothelial injection of botulinum A toxin in patients with non-neurogenic detrusor overactivity refractory to anticholinergics. Urology 2005; **66**:94-98.
20. Parsons CL, Housley T, Schmidt JD, et al: Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994; **73**:504-507.
21. Hanno PM, Sant GR: Clinical highlights of the National Institute of Diabetes and Digestive and Kidney Diseases/Interstitial Cystitis Association scientific conference on interstitial cystitis. Urology 2001; **57(6 Suppl 1)**:2-6.
22. Aoki KR: Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 2003; **43(Suppl 1)**:S9-15.
23. Cui M, Aoki KR: Botulinum toxin type A (BTX-A) reduces inflammatory pain in the rat formalin model. Cephalalgia 2000; **20**:414.
24. Durham PL, Cady R, Cady R: Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: Implications for migraine therapy. Headache 2004; **44**:35-43.
25. Ost D, Roskams T, Van Der Aa F, DeRidder D: Topography of the vanilloid receptor in the human bladder: More than just the nerve fibers. J Urol 2002; **168**:293-297.
26. Birder LA, Kanai AJ, de Groat WC, et al: Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. Proc Natl Acad Sci USA 2001; **98**:13396-13401.
27. Lazzeri M, Vannucchi MG, Zardo C, et al: Immunohistochemical evidence of vanilloid receptor 1 in normal human bladder. Eur Urol 2004; **46**:792-798.
28. Birder LA, Nakamura Y, Kiss S, et al: Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 2002; **5**:856-860.
29. De Groat WC, Kawatani M, Hisamitsu T, et al: Mechanisms underlying the recovery of urinary bladder function following spinal cord injury. J Auton Nerv Syst 1990; **30(Suppl)**:S71-77.
30. Kuo HC: Effectiveness of intravesical resiniferatoxin for anticholinergic treatment refractory detrusor overactivity due to nonspinal cord lesions. J Urol 2003; **170**:835-839.
31. Brady CM, Apostolidis A, Yiangos Y, et al: P2X3-immunoreactive nerve fibers in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin. Eur Urol 2004; **46**:247-253.
32. Silva C, Silva J, Ribeiro MJ, Avelino A, Cruz F: Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor

overactivity of spinal origin: Results of a double-blind randomized placebo-controlled trial. Eur Urol 2005; **48**:650-655.
33. Silva C, Ribeiro MJ, Cruz F: The effect of intravesical resiniferatoxin in patients with idiopathic detrusor instability suggests that involuntary detrusor contractions are triggered by C-fiber input. J Urol 2002; **168**:575-579.
34. Palma PC, Thiel M, Riccetto CL, Dambros M, Miyaoka R, Netto NR Jr: Resiniferatoxin for detrusor instability refractory to anticholinergics. Int Braz J Urol 2004; **30**:53-58.
35. Kuo HC: Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int 2005; **95**:1023-1027.
36. Kuo HC, Liu HT, Yang WC: Therapeutic effect of multiple resiniferatoxin intravesical instillation in patients with refractory detrusor overactivity: A randomized double-blind, placebo controlled study. J Urol 2006; **176**:641-645.
37. Cruz F, Guimaraes M, Silva C, Reis M: Suppression of bladder hyperreflexia by intravesical resiniferatoxin. Lancet 1997; **350**:640-641.
38. Silva C, Rio ME, Cruz F: Desensitization of bladder sensory fibers by intravesical resiniferatoxin, a capsaicin analog: Long-term results for the treatment of detrusor hyperreflexia. Eur Urol 2003; **38**: 444-452.
39. Lazzeri M, Beneforti P, Spinelli M, Zanollo A, Barbagli G, Turini D: Intravesical resiniferatoxin for the treatment of hypersensitive disorder: A randomized placebo controlled study. J Urol 2000; **164**: 676-679.
40. Chai TC, Gray ML, Steers W: The incidence of a positive ice water test in bladder outlet obstructed patients: Evidence for bladder neural plasticity. J Urol 1998; **160**:34-38.
41. Cruz F, Guimaraes M, Silva C, Rio ME, Coimbra A , Reis M: Desensitization of bladder sensory fibers by intravesical capsaicin has long lasting clinical and urodynamic effects in patients with hyperactive or hypersensitive bladder dysfunction. J Urol 1997; **157**:585-589.
42. De Seze M, Wiart L, Joseph PA, Dosquo JP, Mazaux JM, Barat M: Capsicin and neurogenic detrusor hyperreflexia: A double- blind placebo- controlled study in 20 patients with spinal cord lesions. Neurourol Urodyn 1998; **17**:513-523.
43. Igawa Y, Satoh T, Mizusawa H, et al: The role of capsaicin-sensitive afferents in autonomic dysreflexia in patients with spinal cord injury. BJU Int 2003; **91**:637-641.
44. Lazzeri M, Spinelli M, Beneforti P, Zanollo A, Turini D: Urodynamic assessment during intravesical infusion of capsaicin for the treatment of refractory detrusor hyperreflexia. Spinal Cord 1999; **37**:440-443.
45. Cruz F, Guimaraes M, Silva C, Reis M: Intravesical resiniferatoxin, a capsaicin analong, represses bladder hyperreflexia without evoking significant acute discomfort. Lancet 1997; **350**:640-641.
46. Lazzeri M, Beneforti P, Turini D: Urodynamic effects of intravesical resiniferatoxin in humans: Preliminary results in stable and unstable detrusor. J Urol 1997; **158**:2093-2096.
47. Lazzeri M, Spinelli M, Beneforti P, Zanollo A, Turini D: Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord disease. Scand J Urol Nephrol 1998; **32**:331-334.