Novel Treatment of Overactive Bladder Refractory to Antimuscarinic Therapy

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Overactive bladder (OAB) is defined by the International Continence Society as urgency, with or without urge incontinence, usually with frequency (voiding eight or more times in a 24-hour period) and nocturia (awakening two or more times at night to void) [1]. OAB symptoms are frequently associated with involuntary detrusor overactivity, which is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked [1,2]. Patients with OAB symptoms tend to curtail their participation in social activities and are predisposed to depression. Nocturia is associated with sleep disruption and a high risk of falling [3]. Population-based surveys estimate that OAB affects approximately 50 million adults in Europe and the United States. The prevalence increases with age and is associated with high economic and social costs [4,5].

The symptoms of OAB have many possible causes and contributing factors. Urination involves the central nervous system, the spinal cord, and the peripheral autonomic, somatic and sensory afferent innervation of the lower urinary tract and the anatomic components of the lower urinary tract itself. Disorders of any of these structures may contribute to the symptoms of OAB. Thus, the optimal therapy for OAB is decided by a thorough evaluation, followed by treatment of all likely causes and contributing factors. Traditional anticholinergic agents, behavioral interventions and combined therapy are efficacious for treating urge and mixed urge-stress incontinence. However, since the pathophysiology of OAB is multifactorial, there are many potential targets for drugs in the future. The following review is a brief list of novel treatments and some alternatives for OAB refractory to antimuscarinic therapy.

B3-ADRENERGIC RECEPTOR (AR) AGONISTS

The bladder smooth muscle contains β-ARs, and three subtypes (β1, β2, and β3) have been found in most species [6]. A predominant expression of β3-AR mRNA in human detrusor muscle has been shown. Of the three subtypes of β-AR mRNA, β3-AR accounts for 97% and β1-AR and β2-AR for only 1.5% and 1.4% respectively [7]. Non selective β-AR agonists exhibit serious cardiovascular side effects such as tachycardia and decreases in blood pressure by stimulating β1ARs and β2ARs. These side effects should be decreased when using selective agonists. The beta-adrenoceptor-subtype (β2-AR and/or β3-AR) which mainly mediates the relaxation of the urinary bladder depends on the species. The *in vivo* effects of β3-AR agonists on bladder function have been investigated in animal models. β3-AR agonists increase bladder capacity with no change in micturition pressure and residual urine [8]. Preliminary results from human study have shown that β3-AR agonists significantly decrease incontinence episodes when compared with a placebo [9].

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PURINOCEPTOR ANTAGONISTS

Adenosine triphosphate (ATP) can be released by distension of the urinary bladder and released ATP may be able to activate the micturition reflex by inducing nonadrenergic, noncholinergic bladder contraction [10]. ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G protein-coupled receptor family (P2Y). $P2X_3$ receptor functions as a ligand-gated ion channel and may transduce ATP-evoked nociceptor activation [11]. It has been suggested that release of ATP is proportional to the extent of bladder distension in both normal and $P2X_3$-receptor deficient mice. Mouse studies suggest that this receptor is important for peripheral pain responses, and also participates in pathways controlling urinary bladder volume reflexes.

In one study, detrusor $P2X_2$ receptors were significantly increased in female patients with idiopathic detrusor overactivity, while other P2X receptor subtypes were significantly decreased. There was no detectable purinergic component of nerve-mediated detrusor contractility in control bladder biopsy specimens [12]. Recently, some studies have shown that activation of recombinant and native $P2X_3$ and $P2X_{2/3}$ receptors can be inhibited by selective $P2X_3$/$P2X_{2/3}$ antagonists in animal models of chronic inflammatory and neuropathic pain [13]. Thus it is possible that the development of selective antagonists for this receptor may have a therapeutic potential in pain relief and in the treatment of disorders of urine storage.

BLADDER-SELECTIVE PHOSPHODIESTERASE (PDE) INHIBITORS

In lower urinary tract smooth muscle, increases in cyclic adenosine monophosphate (cAMP) is associated with bladder relaxation, and cyclic guanosine monophosphate (cGMP) is important for urethral relaxation. The inactivation of both cAMP and cGMP is mediated by phosphodiesterases (PDEs), which include at least 6 of the 11 isoenzyme families (1-5 and 11) that show functional importance in the management of the lower urinary tract [14]. Truss et al have found that significant relaxation of human detrusor muscle in vitro paralleled by increases in cyclic nucleotide levels is induced by vinpocetine (a non-selective inhibitor of PDE1), suggesting that the cAMP pathway and PED1 may have main roles in regulation of detrusor smooth muscle tone [15]. Kaiho et al have demonstrated that selective PDE 4 inhibitor IC485 and tolterodine tartrate reduce detrusor overactivity in rats with bladder outlet obstruction. In addition, doses of IC485 that suppress

non-voiding contractions had no effect on voiding function [16]. In a clinical open-label study of patients with erectile dysfunction which assessed the impact of sildenafil on the lower urinary tract, Mulhall et al observed that not only the erectile domain of the International Index of Erectile Function but also the total International Prostate Symptom Score improved significantly [17]. Therefore, bladder-selective PDE inhibitors deserve further study as potential agents for treating overactive bladder in patients with benign prostatic hyperplasia.

ENDOTHELIN (ET) RECEPTOR ANTAGONISTS

Three type of endothelins (ET-1, ET-2, ET-3) and two types of ET receptors (ET_A, ET_B) have been demonstrated both in the prostate and bladder. It is also reported that the ET_A receptor is the predominant receptor subtype in the bladder. In the rat urinary bladder, nonadrenergic, noncholinergic neurotransmission is facilitated by ET-1 via the ET_A receptor [18]. Ogawa et al have shown that protein and mRNA levels of ET-1 in the bladder are significantly increased in rats with chronic spinal cord injury (SCI). Inhibition of ET_A receptors, but not ET_B receptors, suppresses bladder overactivity in chronic SCI rats. ABT-627, an ET_A antagonist, can inhibit non-voiding bladder contractions [19]. Schroder et al have found that oral administration of an endothelin converting enzyme inhibitor increases micturition intervals and bladder volume, and decreases nonvoiding contractions and residual urine in bladder outlet obstruction animal models [20]. These findings may indicate that the suppression of ET_A receptors is effective in suppressing not only bladder overactivity of myogenic origin, but also that induced by neurogenic diseases such as SCI. Thus, further clinical evidence is needed and encouraged to demonstrate that ET receptor antagonists are effective against OAB.

RHO-KINASE INHIBITORS

It has been suggested that changes of smooth muscle cell contractility/tone contributes to the lower urinary tract symptoms in patients with OAB. Many therapies have focused mainly on blockade of individual membrane receptors to diminish smooth muscle contractility and provide symptomatic relief. This raises the question of whether there is a common pathway through which the different contractile transmitters/mediators might initiate contraction or alter contractility of the smooth muscle. In the analysis of intracellular signal transduction mechanisms, the regulation of myosin light chain phosphatase (MLCP) has received much attention [21]. In various smooth muscle tissues, including the bladder, regulation of MCLP has been suggested as one of the main mechanisms for increasing Ca^{2+} sensitivity [22]. A main pathway to inhibit MLCP and induce Ca^{2+} sensitization involves Rho-kinase. When MLCP activity is inhibited, the phosphorylated form of myosin light chain (MLC) is maintained and smooth muscle remains contracted. Therefore, the development and use of inhibitors to Rho-kinase have been the most prolific treatment to manipulate the Ca^{2+} sensitivity of smooth muscle.

Recently, Bing et al showed that the Rho-kinase inhibitor Y27632 enhances the relaxation of precontracted detrusor smooth muscle strips from a decompensated bladder. The enhancement of relaxation of the KCl-induced contraction of the decompensated bladder by Y-27632 is associated with dephosphorylation of MLC20 [23]. Morelli et at found that human bladder contraction mainly depends on Ca^{2+} influx via L-type voltage-gated Ca^{2+} channels and on RhoA/Rho kinase contractile signaling, which is upregulated in OAB. Elocalcitol, a vitamin D receptor agonist inhibiting RhoA/Rho kinase signaling, upregulates Ca^{2+} entry through L-type Ca^{2+} channels in human bladder smooth muscle cells, thus balancing its inhibitory effect on RhoA/Rho kinase signaling [24]. Further studies are required to clarify the therapeutic potential of Rho-kinase inhibitors in OAB.

BOTULINUM TOXIN (BTX)

First isolated by van Ermengem in 1897, botulinum toxin (BTX) is the most potent biological toxin known [25]. BTX has wide clinical applicability and usefulness for urological disorders, including detrusorexternal sphincter dyssynergia, neurogenic detrusor overactivity, idiopathic detrusor overactivity, and benign prostatic hyperplasia [26]. In the elderly population, intravesical BTX-A for detrusor overactivity appears to be efficacious and durable with a low incidence of adverse events [27]. However, the procedure for BTX-A injection requires cystoscopic guidance and anesthesia, which may be associated with pain, bleeding and anesthesia risks. Considering that intravesical instillation of chemotherapy agents for patients with bladder cancer is a more comfortable procedure, Chuang et al developed a novel design, "Lipotoxin", which combines liposome and BTX-A [28]. Liposomes are able to deliver BTX-A with efficacy and low toxicity. Intravesical instillation of lipotoxin cleaves SNAP-25 and inhibits calcitonin gene-related peptide release from afferent nerve terminals, and blocks acetic acid-induced hyperactive bladder in rats. The design appears to be a promising therapeutic method for overactive bladder refractory to conventional therapy.

NERVE GROWTH FACTOR (NGF) INHIBITORS

In the urinary tract, NGF is produced by the urothelium and smooth muscle [29]. Clinical and experimental data indicate a direct link between increased levels of NGF in bladder tissue and urine and overactive bladder. Urinary NGF levels are increased in patients with bladder outlet obstruction with OAB symptoms [30]. By contrast, urinary NGF levels decrease in patients with overactive bladder after successful treatment with antimuscarinic agents and detrusor botulinum toxin-A injection [31,32]. Jang et al have shown that intravesical instillation with a cyclooxygenase-2 (COX-2) inhibitor can reduce cyclophosphamide induced OAB. Thus intravesical instillation with a COX-2 inhibitor can be considered a possible treatment for overactive bladder [33]. However, to our knowledge, NGF inhibitor is not currently available as a novel treatment of overactive bladder and is still under investigation.

GLUTAMIC ACID DECARBOXYLASE GENE THERAPY

Glycine and gamma-aminobutyric acid (GABA) inhibitory mechanisms have been identified in the rat spinal cord in local interneuronal inhibitory pathways projecting directly to the periganglia neurons. Intrathecal injection of $GABA_A$ or $GABA_B$ agonists increase bladder capacity and decrease voiding pressure and efficiency in rats [34]. Miyazato et al have shown that expression of glutamate decarboxylase (GAD), a GABA synthesizing enzyme, is decreased in rats with spinal cord injury [35]. Therefore, stimulation of spinal GABAergic mechanisms could be effective for the treatment of detrusor overactivity after

spinal cord injury. However, systemic or intrathecal application of GABA receptor agonists inhibits not only detrusor overactivity, but also bladder efferent activity to reduce bladder contractility. Recently, gene therapy using the herpes simplex virus delivered glutamic acid decarboxylase (HSV-GAD) vectors via injection into the bladder and this was carried through bladder afferent pathways to express GAD genes and release GABA in the spinal cord [36]. GAD gene therapy mainly inhibits detrusor overactivity mediated by C-fiber bladder afferent pathways via activation of $GABA_A$ receptors. Thus, HSV-based GAD gene transfer to bladder afferent pathways may represent a novel approach for the treatment of neurogenic detrusor overactivity.

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