Prospective pharmacologic therapies for the overactive bladder

Karl-Erik Andersson

Ther Adv Urol

[2009] 1(2) 71–83

DOI: 10.1177/
1756287209103937

© The Author(s), 2009.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Lower urinary tract symptoms (LUTS), overactive bladder syndrome (OAB) and detrusor overactivity (DO) are all conditions that can have major effects on quality of life and social functioning. Antimuscarinic drugs are first-line treatment—they often have good initial response rates, but adverse effects and decreasing efficacy cause long-term compliance problems, and alternatives are needed. The recognition of the functional contribution of the urothelium, the spontaneous myocyte activity during bladder filling, and the diversity of nerve transmitters has sparked interest in both peripheral and central modulation of LUTS/OAB/DO pathophysiology. There may be several new possibilities to treat LUTS/OAB/DO. β_3 -AR agonists (YM178), PDE 5 inhibitors (sildenafil, tadalafil, vardenafil), vitamin D analogs (elocalcitol), combinations (α_1 -AR antagonist + antimuscarinic), and drugs with a central mode of action (tramadol, aprepitant) all have Randomized controlled trial (RCT) documented efficacy. Which of these therapeutic principles will be developed to clinically useful treatments remains to be established.

Keywords: incontinence, detrusor overactivity, drug treatment

Introduction

The search for new pharmacologic therapies to treat voiding disorders, including the overactive bladder (OAB) syndrome has been intensive. Many new drugs aimed at micturition control have been suggested and discussed, and current research has revealed a number of peripheral and central mechanisms involved in the regulation of both normal and dysfunctional micturition [Drake 2008; Sacco *et al.* 2008; Yoshimura *et al.* 2008; Andersson 2007; Colli *et al.* 2007]. Some of these mechanisms may be realistic targets for drugs, but there is a difficulty in separating such mechanisms from ‘dead ends’. Signals obtained in preclinical models must be critically analysed and not interpreted based on wishful thinking, keeping in mind the large number of steps between a pre-clinical signal and a drug candidate. Some drugs, representing different principles, for which there is a reasonable rationale for use, and for which proof of principle studies have been positive, are the focus of this review. In addition, some interesting future research directions are briefly discussed.

An extensive evaluation and discussion of current OAB therapies was recently performed by the

4th International Consultation on Incontinence [Andersson *et al.* in press; Tables 1 and 2].

Background

OAB is common and has a multifactorial pathophysiology, implying that it is difficult to conceive that one drug or drug principle would be effective (enough) in all patients with OAB symptoms (Figure 1). Irwin *et al.* [2006], studying 19,000 adult men and women, found that the prevalence in both men and women was around 12% and that it increases with age. The OAB syndrome has often been assumed to be caused by detrusor overactivity (DO), even if this not always seems to be the case [Aschkenazi *et al.* 2007; Hashim and Abrams 2004; Digesu *et al.* 2003; Hyman *et al.* 2001]. Irrespective of the pathophysiology, the goal of treatment of idiopathic OAB symptoms with and without DO is to obtain symptom relief without interfering with the emptying ability. Although our understanding regarding bladder function has increased during recent years, the detrusor muscle and its functional regulation still provide considerable research challenges. The detrusor muscle itself has for many

Correspondence to:

Karl-Erik Andersson,
MD, PhD

Wake Forest Institute for
Regenerative Medicine,
Wake Forest University
School of Medicine,
Medical Center Boulevard,
Winston Salem, NC 27157,
USA
keanders@wfubmc.edu

Table 1. Oxford guidelines (modified), 4th International Consultation on Incontinence, Paris, July, 2008.**Levels of evidence**

- Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs)
- Level 2: RCTs, good quality prospective cohort studies
- Level 3: Case-control studies, case series
- Level 4: Expert opinion

Grades of recommendation

- Grade A: Based on level 1 evidence (highly recommended)
- Grade B: Consistent level 2 or 3 evidence (recommended)
- Grade C: Level 4 studies or "majority evidence" (optional)
- Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

Table 2. Drugs used in the treatment of OAB/DO. Assessments according to the Oxford system (modified), 4th International Consultation on Incontinence, Paris, July, 2008.

	Level of evidence	Grade of recommendation
Antimuscarinic drugs		
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Fesoterodine	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs acting on membrane channels		
Calcium antagonists	2	D
K-Channel openers	2	D
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Dicyclomine	3	C
Flavoxate	2	D
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
Alpha-AR antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Beta-AR antagonists		
Terbutaline (beta 2)	3	C
Salbutamol (beta 2)	3	C
YM-178 (beta 3)	2	B
PDE-5 Inhibitors⁺		
(Sildenafil, Tadalafil, Vardenafil)	2	B
COX-inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)***	2	A
Botulinum toxin (idiopathic)***	3	B
Capsaicin (neurogenic)**	2	C
Resiniferatoxin (neurogenic)**	2	C
Other drugs		
Baclofen*	3	C
Hormones		
Estrogen	2	C
Desmopressin [#]	1	A

⁺(male LUTS/OAB); *intrathecal; **intravesical; ***bladder wall; [#]nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!

Figure 1. Pathophysiology of the overactive bladder.

years been the target for drug treatment. However, depression of detrusor contractility, resulting in a reduced ability to empty the bladder, has not produced any success in the treatment of voiding dysfunction and focus has changed to other bladder structures/mechanisms, such as urothelial signaling and afferent nerves as targets for intervention [Birder and de Groat 2007; Andersson 2002]. There is also an emerging interest for drugs acting in the central nervous system [Andersson and Pehrson 2003].

β_3 -Adrenoceptor (AR) agonists

It has been known for a long time that β -adrenoceptor (AR) agonists can inhibit bladder contractions [Andersson, 1993], but the principle was considered therapeutically uninteresting for OAB/DO treatment because of cardiac side effects. The three defined β -AR subtypes (β_1 , β_2 , and β_3) have been identified in the detrusor of most species [Michel and Vrydag, 2006; Andersson and Arner, 2004]. Also the human urothelium contains all three receptor subtypes [Otsuka *et al.* 2008], but in both detrusor and urothelium there is a predominant expression of β_3 -AR mRNA [Michel and Vrydag, 2006; Nomiya and Yamaguchi, 2003] and there is convincing evidence from both normal and neurogenic bladders that these receptors are functionally active [Leon *et al.* 2008; Badawi *et al.* 2007; Biers *et al.* 2006; Michel and Vrydag, 2006; Igawa *et al.* 2001; Morita *et al.* 2000; Fujumura *et al.* 1999; Igawa *et al.* 1999; Takeda *et al.* 1999]. The human

detrusor also contains β_2 -ARs, and most probably both receptor subtypes are involved in the physiological effects (relaxation) of noradrenaline in this structure [Michel and Vrydag, 2006; Andersson and Arner 2004].

The generally accepted mechanism, by which β -ARs induce detrusor relaxation in most species, is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder K⁺ channels, particularly BK_{ca} channels, may be more important in β -AR mediated relaxation than cAMP [Frazier *et al.* 2008; Frazier *et al.* 2005; Uchida *et al.* 2005; Hudman *et al.* 2000].

The in vivo effects of β_3 -AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β_3 -AR agonists increase bladder capacity with no change in micturition pressure and residual volume [Kaidoh *et al.* 2002; Takeda *et al.* 2002; Woods *et al.* 2001; Fujimura *et al.* 1999]. For example, Hicks *et al.* [2007] studied the effects of the selective β_3 -AR agonist, GW427353, in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid evoked bladder hyperactivity, without affecting voiding.

A number of β_3 -AR selective agonists are currently being evaluated as potential treatment for

OAB in humans including GW427353 and YM178 [Colli *et al.* 2007]. Takasu *et al.* [2007] reported that the selective β_3 -AR agonist, YM187, mediated muscle relaxation in human bladder strips. Chapple *et al.* [2008] reported the results of a placebo controlled clinical trial with this drug in patients with OAB. The primary efficacy analysis showed a statistically significant reduction in mean micturition frequency, compared to placebo. With respect to secondary variables YM178 was significantly superior to placebo concerning mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urgency incontinence episodes, and urgency episodes per 24 hours. The drug was well tolerated, and the most commonly reported side effects were headache and gastrointestinal adverse effects. The results of this well-conducted proof of concept study showed that the principle of β_3 -AR agonism may be useful for treatment of patients with OAB.

The positive effects of β_3 -AR agonists on DO in several animal models were obtained without affecting the ability to empty the bladder, and this was obviously also the case in the patient study of Chapple *et al.* [2008]. This would mean that β_3 -AR agonists do not interfere with the voiding contraction. Thus, the basic requirement of an OAB drug – elimination of symptoms and involuntary bladder contractions without effects on emptying – seems to be fulfilled. However, to show that β_3 -AR agonists offer a viable therapeutic alternative or complement to current treatments of OAB/DO requires further well designed RCTs.

Phosphodiesterase (PDE) inhibitors

It is generally considered that drugs acting through the NO/cGMP system preferably relax the smooth muscle of the bladder outflow region [Andersson and Arner, 2004], whereas drugs stimulating the generation of cAMP relax both the detrusor and the outflow region [Andersson and Arner, 2004; Andersson, 1999]. Providing that drugs producing relaxation of LUT smooth muscle would be effective in the treatment of OAB/DO, use of PDE inhibitors to enhance the cAMP- and cGMP-mediated relaxation of detrusor, prostate and urethral smooth muscle should then be a logical approach (Andersson, 2007). There should be no lack of alternatives since there are presently 11 PDE

families, some of which preferentially hydrolyse either cAMP or cGMP [Andersson, 2007]. Uckert *et al.* [2001] investigating human bladder tissue, found messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. Truss *et al.* [2001; 2000] presented clinical data with vinpocetine (a low affinity inhibitor of PDE 1) in patients with urgency/urgency incontinence or low compliance bladders. However, vinpocetine only caused statistically significant results for one parameter [Truss *et al.* 2001]. Studies with other PDE 1 inhibitors than vinpocetin (which may not be an optimal drug for elucidation the principle) do not seem to have been performed.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the *in vitro* contractile response of guinea pig [Longhurst *et al.* 1997] and rat [Kaiho *et al.* 2008; Nishiguchi *et al.* 2007] bladder strips, and also suppressed rhythmic bladder contractions of the isolated guinea pig bladder [Gillespie 2004]. Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose-limiting effect [Giembycz 2005]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

The observation that patients treated for erectile dysfunction with PDE 5 inhibitors had an improvement of their LUTS, has sparked a new interest in also using these drugs for treatment of LUTS and OAB. After the report in an open study [Sairam *et al.* 2002] that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS, this observation has been confirmed in several well designed and conducted RCTs [Stief *et al.* 2008; McVary *et al.* 2007 a, b].

The mechanism behind the beneficial effect of the PDE 5 inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. The drugs obviously do not interfere with the emptying ability of the bladder, and thus do not reduce the contractility of the detrusor muscle in response to parasympathetic (mainly cholinergic) activation. Like the β_3 -AR agonists, the PDE 5 inhibitors seem to act mainly during bladder filling. If the main site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should

Figure 2. Effects of a β_3 -adrenoceptor agonist (YM-178) on urgency episodes (≥ 3)/24 h in patients with overactive bladder. Mean change from baseline to endpoint. Chapple *et al.* EAU 2008, poster presentation.

be expected. Such an effect was not found in the trials referred to. However, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstitial cells, and suburothelial afferent nerves).

The beneficial effects of PDE 5 inhibitors have so far been demonstrated in male LUTS/OAB. Ongoing trials will reveal whether or not these drugs are therapeutic OAB/DO alternative in females.

Vitamin D₃ receptor analogues

Crescioli *et al.* [2005] demonstrated that rat and human bladders expressed receptors for vitamin D₃. In a rat model of partial bladder outflow obstruction, Schröder *et al.* [2006] showed that an analogue of vitamin D₃, elocalcitol (BXL-628), at non-hypercalcemic doses, reduced both frequency and amplitude of non-voiding contractions (Figure 2). Drug treatment did not prevent bladder hypertrophy, but reduced the damage to the bladder smooth muscle which occurs with increasing bladder weight in this model. The mechanism of action for the effects has not been clarified. Analogues of vitamin D₃ have been shown to inhibit BPH cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [Crescioli *et al.* 2004; 2003; 2002]. However, elocalcitol was also shown to have an inhibitory effect on the RhoA/Rho kinase pathway [Morelli *et al.* 2007]. Upregulation of this pathway has been associated with bladder changes associated

with diabetes, outflow obstruction, and DO [Christ and Andersson, 2007; Peters *et al.* 2006].

In an RCT enrolling 120 female patients with OAB, where the primary endpoint was an increase in the mean volume voided, treatment with elocalcitol produced a significant increase *versus* placebo was demonstrated [Colli *et al.* 2007]. The side effect profile of the drug is attractive—compared to placebo no adverse effects were demonstrated [Colli *et al.* 2007]. Irrespective of whether or not inhibition of the RhoA/Rho kinase pathway is the main mechanism by which elocalcitol (and vitamin D₃ receptor agonists?) affects bladder function, it remains to be established if the drug (monotherapy or in combination) will be a useful alternative for the treatment of OAB/DO.

Centrally acting drugs

Many parts of the brain seem to be activated during storage and voiding [Fowler *et al.* 2008; Griffiths and Tadic 2008; Griffiths 2007], and there is increasing interest in drugs modulating the micturition reflex by a central action [Andersson and Pehrson 2003]. Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples. However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OAB, since selective actions may be difficult to obtain. Holstege [2005], reviewing some of the central mechanisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that ‘the problem in

Figure 3. Effects of elocalcitol (BXL-628) on frequency and amplitude of spontaneous, non-voiding contractions in sham-operated vehicle (SV) and drug-treated rats (SD) compared to obstructed vehicle (BV) and drug-treated (BD) rats. Schröder *et al.* 2006.

OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level.⁷

Gabapentin

Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [Striano and Striano 2008]. It was originally designed as an anticonvulsant GABA (γ -aminobutyric acid) mimetic capable of crossing the blood-brain barrier [Maneuf *et al.* 2003]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [Maneuf *et al.* 2003]. It has been suggested that it acts by binding to a subunit of the $\alpha_2\delta$ unit of voltage dependent calcium channels [Striano and Striano 2008; Gee *et al.* 1996]. Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone *et al.* [2006] reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim *et al.* [2004] studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well-tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities

have failed. It is possible that gabapentin and other $\alpha_2\delta$ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives.

Tramadol

Tramadol is a well-known analgesic drug [Grond and Sablotzski 2004]. By itself, it is a weak μ -receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ -receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and noradrenaline reuptake [Grond and Sablotzski 2004]. This profile is of particular interest, since both μ -receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS/OAB/DO, as shown in a placebo controlled study with duloxetine [Steers *et al.* 2007].

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction [Pehrson *et al.* 2003]. Tramadol also inhibited DO induced by apomorphine in rats [Pehrson and Andersson 2003; Figure 3] – a crude model of bladder dysfunction in Parkinson's disease. Singh *et al.* [2008] gave tramadol epidurally and found the drug to increase bladder capacity and compliance, and to delay filling sensations without ill effects on voiding. Safarinejad and Hosseini [2006] evaluated in a double-blind placebo-controlled randomized study, the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years of age or older were given 100mg tramadol sustained release every 12h for 12 weeks. Clinical evaluation was performed at baseline and every 2 weeks during treatment. Tramadol significantly reduced the number of incontinence periods and induced significant improvements in urodynamic parameters. The main adverse effect was nausea. It was

Figure 4. Effects of 100 µg kg⁻¹ apomorphine given subcutaneously (s.c.) to female rat pretreated with intravenous saline (A) or 5 mg kg⁻¹ tramadol intravenously (i.v.) (B). Upper tracings show bladder pressure. Lower tracings show voided volume. Pehrson and Andersson, 2003.

concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the best suitable drug for treatment of OAB/DO (as judged from the side effect profile from pain treatment—constipation, nausea, dizziness and somnolence; Mongin 2007), the study proves the principle of modulating micturition via the μ -receptor.

NK1-receptor antagonists

The main endogenous tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control [Covenas *et al.* 2003; Saffroy *et al.* 2003; Lecci and Maggi 2001]. NK1 receptor expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via

NK1 receptors in the micturition reflex induced by bladder filling has been demonstrated [Ishizuka *et al.* 1994] in normal rats and more clearly in rats with bladder hypertrophy secondary to BOO. Capsaicin-induced detrusor overactivity was reduced by blocking NK1 receptor-expressing neurons in the spinal cord, using intrathecally administered substance P-saponin conjugate [Seki *et al.* 2005]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka *et al.* 1995].

In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses, and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction [Gu *et al.* 2000]. Intracerebroventricular administration of NK1 and NK2 receptor antagonists to awake

rats suppressed detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka *et al.* 2000]. Taken together, available information suggests that spinal and supraspinal NK1 and NK2 receptors may be involved in micturition control.

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting [Massaro and Lenz 2005], significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), as shown in a well designed pilot RCT [Green *et al.* 2006]. The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total urinary incontinence and urgency incontinence episodes, and urgency episodes. Aprepitant significantly decreased the average daily number of micturitions compared with placebo at 8 weeks. The average daily number of urgency episodes was also significantly reduced compared to placebo, and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. Aprepitant was generally well-tolerated and the incidence of side effects, including dry mouth, was low. The results of this initial proof of concept study suggest that NK-1 receptor antagonism holds promise as a potential treatment approach for OAB.

Alternative strategies – combinations

Combining the current α_1 -adrenoceptor antagonists with other agents might theoretically provide improved symptom relief. One such example is the combination of α_1 -adrenoceptor antagonists with 5 alpha reductase inhibitors, which has proven to improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery [Roehrborn *et al.* 2008; McConnell *et al.* 2003]. Other combinations have also been tested with varying degrees of success. Traditionally muscarinic receptor antagonists have been contradicted in patients with BPH due to fears of urinary retention. However, this dogma has been questioned and several studies have been performed in which α_1 -adrenoceptor antagonists are combined with muscarinic receptor antagonists

with promising results [Rovner *et al.* 2008; McVary, 2007; Kaplan *et al.* 2006; Novara *et al.* 2006; Ruggieri *et al.* 2005; Lee *et al.* 2005; 2004; Athanasopoulos *et al.* 2003]. Speculatively, several other combinations can be suggested [Andersson, 2008].

Future directions

The endocannabinoid system has received widespread attention as a pharmacotherapeutic target to modulate physiological and pathophysiological conditions also in the bladder. Hiragata *et al.* [2007] showed that ajulemic acid, a mixed CB1/CB2 receptor agonist, can suppress normal bladder activity and urinary frequency induced by bladder nociceptive stimuli. The inhibitory effects were inhibited by AM251, a selective CB1 receptor antagonist. These findings suggest that cannabinoid receptor agonists may have a potential as therapeutic agents in DO.

An exciting finding is that TRPV1 receptor antagonists have potentially useful effects on micturition in animal model [Cruz *et al.* 2008]. Two other TRPs may also have a role in bladder function. TRPA1 receptors were shown to be expressed in C-fiber afferents as well as urothelium and interstitial cells, both in the bladder and urethra, and also to affect micturition [Gratzke *et al.* 2008; Streng *et al.* 2008; Du *et al.* 2007]. Of interest is the finding that hydrogen sulfide, which may be formed endogenously during infection/inflammation, is an activator of TRPA1. Another member of the TRP family, the TRPV4 receptor (channel), can be activated by hypo-osmolarity, heat or certain lipid compounds, and seems to be expressed mainly by urothelial cells. In mice deletion of this channel results in impaired voiding responses [Gevaert *et al.* 2007] and intravesical instillation of a TRPV4 agonist in the rat triggered a novel voiding reflex, which could regulate the late phase of contraction [Birder *et al.* 2007]. In the conscious ewe, TRPV4 may also be involved in a urethra to bladder reflex, proposed to facilitate bladder emptying [Combrisson *et al.* 2007]. The roles of TRPA1 and TRPV4 in the normal and pathological bladder have to be established. Whether or not antagonists of these receptors could be potential targets for drugs aimed for treatment of LUTS/OAB/DO can only be speculated on.

Conclusions

There may be several new possibilities to treat LUTS/OAB/DO. β_3 -AR agonists (YM178), PDE 5 inhibitors (sildenafil, tadalafil, vardenafil), vitamin D analogs (elocalcitol), combinations (α_1 -AR antagonist + antimuscarinic), and drugs with a central mode of action (tramadol, aprepitant) all have RCT documented efficacy. Which of these therapeutic principles will be developed to clinically useful treatments remains to be established.

Conflict of interest statement

The author consults for Astellas, Novartis, Procter & Gamble, Pfizer, BioXell and Sanofi-Aventis.

References

- Andersson, K.E. (1993) Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. *Pharmacol Rev* 45: 253–308.
- Andersson, K.E. (1999) Pathways for Relaxation of detrusor smooth muscle, in Baskin, L.S. and Hayward, S.W. (eds) *Advances in Bladder Research*. Kluwer Academic/Plenum Publishers: New York, 241–252.
- Andersson, K.E. (2002) Bladder activation: afferent mechanisms. *Urology* 59(5 Suppl 1): 43–50.
- Andersson, K.E. (2003) Storage and voiding symptoms: pathophysiologic aspects. *Urology* 62: 3–10.
- Andersson, K.E. (2007) LUTS treatment: future treatment options. *Neurourol Urodyn* 26: 934–47.
- Andersson, K.E. (2008) How many drugs for LUTS due to BPH are too many? *J Urol* 180: 811–2.
- Andersson, K.E. and Arner, A. (2004) Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev* 84: 935–86.
- Andersson, K. E., Chapple, C. R., Cardozo, L., Cruz, F., Hashim, H., Michel, M. C. *et al.* (in press) Pharmacological treatment of urinary incontinence, P. Abrams, L. Cardozo, S. Khoury, & A. Wein (eds) *Incontinence, 4th International Consultation on Incontinence*. Plymouth Distributors Ltd: Plymouth, UK.
- Andersson, K.E. and Pehrson, R. (2003) CNS involvement in overactive bladder: pathophysiology and opportunities for pharmacological intervention. *Drugs* 63: 2595–611.
- Aschkenazi, S., Botros, S., Miller, J., Gamble, T., Sand, P. and Goldberg, R. (2007) Overactive bladder symptoms are not related to detrusor overactivity. *Neurourol Urodyn* 26: 35.
- Athanasopoulos, A., Gyftopoulos, K., Giannitsas, K., Fisfis, J., Perimenis, P. and Barbalias, G. (2003) Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol* 169: 2253–6.
- Badawi, J.K., Seja, T., Uccellehan, H., Honeck, P., Kwon, S.T., Bross, S. *et al.* (2007) Relaxation of human detrusor muscle by selective beta-2 and beta-3 agonists and endogenous catecholamines. *Urology* 69: 785–90.
- Biers, S.M., Reynard, J.M. and Brading, A.F. (2006) The effects of a new selective beta3-adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder. *BJU Int* 98: 1310–14.
- Birder, L.A. and de Groat, W.C. (2007) Mechanisms of disease: involvement of the urothelium in bladder dysfunction. *Nat Clin Pract Urol* 4: 46–54.
- Birder, L., Kullmann, F.A., Lee, H., Barrick, S., de Groat, W., Kanai, A. *et al.* (2007) Activation of urothelial transient receptor potential vanilloid 4 by 4alpha-phorbol 12,13-didecanoate contributes to altered bladder reflexes in the rat. *J Pharmacol Exp Ther* 323: 227–35.
- Carbone, A., Palleschi, G., Conte, A., Bova, G., Iacovelli, E., Bettolo, R.M. *et al.* (2006) Gabapentin treatment of neurogenic overactive bladder. *Clin Neuropharmacol* 29: 206–14.
- Chapple, C.R., Yamaguchi, O., Ridder, A., Liehne, J., Carl, S., Mattiassin, A. *et al.* (2008) Clinical proof of concept study (Blossom) shows novel B3 adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms of overactive bladder. *Eur Urol Suppl* 7: 239.
- Christ, G.J. and Andersson, K.E. (2007) Rho-kinase and effects of Rho-kinase inhibition on the lower urinary tract. *Neurourol Urodyn* 26: 948–54.
- Colli, E., Digesu, G.A. and Olivieri, L. (2007) Overactive bladder treatments in early phase clinical trials. *Expert Opin Investig Drugs* 16: 999–1007.
- Combrisson, H., Allix, S. and Robain, G. (2007) Influence of temperature on urethra to bladder micturition reflex in the awake ewe. *Neurourol Urodyn* 26: 290–5.
- Covenas, R., Martin, F., Belda, M., Smith, V., Salinas, P., Rivada, E. *et al.* (2003) Mapping of neurokinin-like immunoreactivity in the human brainstem. *BMC Neurosci* 4: 3.
- Crescioli, C., Ferruzzi, P., Caporali, A., Scaltriti, M., Bettuzzi, S., Mancina, R. *et al.* (2002) Des (1-3) IGF-I-stimulated growth of human stromal BPH cells is inhibited by a vitamin D3 analogue. *Mol Cell Endocrinol* 198: 69–75.
- Crescioli, C., Ferruzzi, P., Caporali, A., Mancina, R., Comerci, A., Muratori, M. *et al.* (2003) Inhibition of spontaneous and androgen-induced prostate growth by a nonhypercalcemic calcitriol analog. *Endocrinology* 144: 3046–57.

- Crescioli, C., Ferruzzi, P., Caporali, A., Scaltriti, M., Bettuzzi, S., Mancina, R. *et al.* (2004) Inhibition of prostate cell growth by BXL-628, a calcitriol analogue selected for a phase II clinical trial in patients with benign prostate hyperplasia. *Eur J Endocrinol* 150: 591–603.
- Crescioli, C., Morelli, A., Adorini, L., Ferruzzi, P., Luconi, M., Vannelli, G.B. *et al.* (2005) Human bladder as a novel target for vitamin D receptor ligands. *J Clin Endocrinol Metab* 90: 962–72.
- Cruz, F., Charrua, A., Cruz, C., Gharat, L., Gullapalli, S., Narayanan, S. *et al.* (2008) GRC 6211, a new oral TROV1 antagonist, decreases the frequency of bladder reflex contractions and noxious input in rats with acute or chronic cystitis. *Eur Urol Suppl* 7: 181.
- Digesu, G.A., Khullar, V., Cardozo, L. and Salvatores, S. (2003) Overactive bladder symptoms: do we need urodynamics? *Neurourol Urodyn* 22: 105–8.
- Drake, M.J. (2008) Emerging drugs for treatment of overactive bladder and detrusor overactivity. *Expert Opin Emerg Drugs* 13: 431–46.
- Du, S., Araki, I., Yoshiyama, M., Nomura, T. and Takeda, M. (2007) Transient receptor potential channel A1 involved in sensory transduction of rat urinary bladder through C-fiber pathway. *Urology* 70: 826–31.
- Fowler, C.J., Griffiths, D. and de Groat, W.C. (2008) The neural control of micturition. *Nat Rev Neurosci* 9: 453–66.
- Frazier, E.P., Mathy, M.J., Peters, S.L. and Michel, M.C. (2005) Does cyclic AMP mediate rat urinary bladder relaxation by isoproterenol? *J Pharmacol Exp Ther* 313: 260–7.
- Frazier, E.P., Peters, S.L., Braverman, A.S., Ruggieri Sr, M.R. and Michel, M.C. (2008) Signal transduction underlying the control of urinary bladder smooth muscle tone by muscarinic receptors and beta-adrenoceptors. *Naunyn Schmiedebergs Arch Pharmacol* 377: 449–62.
- Fujimura, T., Tamura, K., Tsutsumi, T., Yamamoto, T., Nakamura, K., Koibuchi, Y. *et al.* (1999) Expression and possible functional role of the beta3-adrenoceptor in human and rat detrusor muscle. *J Urol* 161: 680–5.
- Gee, N.S., Brown, J.P., Dissanayake, V.U., Offord, J., Thurlow, R. and Woodruff, G.N. (1996) The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem* 271: 5768–76.
- Gevaert, T., Vriens, J., Segal, A., Everaerts, W., Roskams, T., Talavera, K. *et al.* (2007) Deletion of the transient receptor potential cation channel TRPV4 impairs murine bladder voiding. *J Clin Invest* 117: 3453–62.
- Giembycz, M.A. (2005) Life after PDE4: overcoming adverse events with dual-specificity phosphodiesterase inhibitors. *Curr Opin Pharmacol* 5: 238–44.
- Gillespie, J.L. (2004) Phosphodiesterase-linked inhibition of nonmicturition activity in the isolated bladder. *BJU Int* 93: 1325–32.
- Gratzke, C., Streng, T., Waldkirch, E., Sigl, K., Stief, C., Andersson, K.E. *et al.* (2009) Transient Receptor Potential A1 (TRPA1) Activity in the Human Urethra-Evidence for a Functional Role for TRPA1 in the Outflow Region. *Eur Urol* 55: 696–704.
- Green, S.A., Alon, A., Ianus, J., McNaughton, K.S., Tozzi, C.A. and Reiss, T.F. (2006) Efficacy and safety of a neurokinin-1 receptor antagonist in postmenopausal women with overactive bladder with urge urinary incontinence. *J Urol* 176: 2535–40.
- Griffiths, D. (2007) Imaging bladder sensations. *Neurourol Urodyn* 26: 899–903.
- Griffiths, D. and Tadic, S.D. (2008) Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. *Neurourol Urodyn* 27: 466–74.
- Grond, S. and Sablotzki, A. (2004) Clinical pharmacology of tramadol. *Clin Pharmacokinet* 43: 879–923.
- Gu, B.J., Ishizuka, O., Igawa, Y., Nishizawa, O. and Andersson, K.E. (2000) Role of supraspinal tachykinins for micturition in conscious rats with and without bladder outlet obstruction. *Naunyn Schmiedebergs Arch Pharmacol* 361: 543–8.
- Hashim, H. and Abrams, P. (2004) Do symptoms of overactive bladder predict urodynamics detrusor overactivity? *NeuroUrol Urodyn* 23: 484–486.
- Hicks, A., McCafferty, G.P., Riedel, E., Aiyar, N., Pullen, M., Evans, C. *et al.* (2007) GW427353 (solabegron), a novel, selective beta3-adrenergic receptor agonist, evokes bladder relaxation and increases micturition reflex threshold in the dog. *J Pharmacol Exp Ther* 323: 202–9.
- Hiragata, S., Ogawa, T., Hayashi, Y., Tyagi, P., Seki, S., Nishizawa, O. *et al.* (2007) Effects of IP-751, ajulemic acid, on bladder overactivity induced by bladder irritation in rats. *Urology* 70: 202–208.
- Holstege, G. (2005) Micturition and the soul. *J Comp Neurol* 493: 15–20.
- Hudman, D., Elliott, R.A. and Norman, R.I. (2000) K(ATP) channels mediate the beta(2)-adrenoceptor agonist-induced relaxation of rat detrusor muscle. *Eur J Pharmacol* 397: 169–76.
- Hyman, M.J., Groutz, A. and Blaivas, J.G. (2001) Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. *J Urol* 166: 550–2.
- Igawa, Y., Yamazaki, Y., Takeda, H., Hayakawa, K., Akahane, M., Ajisawa, Y. *et al.* (1999) Functional and molecular biological evidence for a possible beta3-adrenoceptor in the human detrusor muscle. *Br J Pharmacol* 126: 819–25.
- Igawa, Y., Yamazaki, Y., Takeda, H., Kaidoh, K., Akahane, M., Ajisawa, Y. *et al.* (2001) Relaxant effects

- of isoproterenol and selective beta3-adrenoceptor agonists on normal, low compliant and hyperreflexic human bladders. *J Urol* 165: 240–4.
- Irwin, D.E., Milsom, I., Hunskaar, S., Reilly, K., Kopp, Z., Herschorn, S. *et al.* (2006) Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 50: 1306–14.
- Ishizuka, O., Igawa, Y., Lecci, A., Maggi, C.A., Mattiasson, A. and Andersson, K.E. (1994) Role of intrathecal tachykinins for micturition in unanaesthetized rats with and without bladder outlet obstruction. *Br J Pharmacol* 113: 111–6.
- Ishizuka, O., Igawa, Y., Nishizawa, O. and Andersson, K.E. (2000) Role of supraspinal tachykinins for volume- and L-dopa-induced bladder activity in normal conscious rats. *NeuroUrol Urodyn* 19: 101–9.
- Ishizuka, O., Mattiasson, A. and Andersson, K.E. (1995) Effects of neurokinin receptor antagonists on L-dopa induced bladder hyperactivity in normal conscious rats. *J Urol* 154: 1548–51.
- Kaidoh, K., Igawa, Y., Takeda, H., Yamazaki, Y., Akahane, S., Miyata, H. *et al.* (2002) Effects of selective beta2 and beta3-adrenoceptor agonists on detrusor hyperreflexia in conscious cerebral infarcted rats. *J Urol* 168: 1247–52.
- Kaiho, Y., Nishiguchi, J., Kwon, D.D., Chancellor, M.B., Arai, Y., Snyder, P.B. *et al.* (2008) The effects of a type 4 phosphodiesterase inhibitor and the muscarinic cholinergic antagonist tolterodine tartrate on detrusor overactivity in female rats with bladder outlet obstruction. *BJU Int* 101: 615–20.
- Kaplan, S.A., Roehrborn, C.G., Rovner, E.S., Carlsson, M., Bavendam, T. and Guan, Z. (2006) Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 296: 2319–28.
- Kim, Y.T., Kwon, D.D., Kim, J., Kim, D.K., Lee, J. Y. and Chancellor, M.B. (2004) Gabapentin for overactive bladder and nocturia after anticholinergic failure. *Int Braz J Urol* 30: 275–8.
- Lecci, A. and Maggi, C.A. (2001) Tachykinins as modulators of the micturition reflex in the central and peripheral nervous system. *Regul Pept* 101: 1–18.
- Lee, K.S., Choo, M.S., Kim, D.Y., Kim, J.C., Kim, H.J., Min, K.S. *et al.* (2005) Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. *J Urol* 174: 1334–8.
- Lee, J.Y., Kim, H.W., Lee, S.J., Koh, J.S. and Suh, H.J. (2004) Chancellor MB. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int* 94: 817–20.
- Leon, L.A., Hoffman, B.E., Gardner, S.D., Laping, N.J., Evans, C., Lashinger, E.S. *et al.* (2008) Effects of the beta 3-adrenergic receptor agonist disodium 5-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate (CL-316243) on bladder micturition reflex in spontaneously hypertensive rats. *J Pharmacol Exp Ther* 326: 178–85.
- Longhurst, P.A., Briscoe, J.A., Rosenberg, D.J. and Leggett, R.E. (1997) The role of cyclic nucleotides in guinea-pig bladder contractility. *Br J Pharmacol* 121: 1665–72.
- Maneuf, Y.P., Gonzalez, M.I., Sutton, K.S., Chung, F.Z., Pinnock, R.D. and Lee, K. (2003) Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cell Mol Life Sci* 60: 742–50.
- Massaro, A.M. and Lenz, K.L. (2005) Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother* 39: 77–85.
- McConnell, J.D., Roehrborn, C.G., Bautista, O.M., Andriole Jr, G.L., Dixon, C.M., Kusek, J.W. *et al.* (2003) Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 349: 2387–98.
- McVary, K.T. (2007) A review of combination therapy in patients with benign prostatic hyperplasia. *Clin Ther* 29: 387–98.
- McVary, K.T., Roehrborn, C.G., Kaminetsky, J.C., Auerbach, S.M., Wachs, B., Young, J.M. *et al.* (2007a) Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 177: 1401–7.
- McVary, K.T., Monnig, W., Camps Jr, J.L., Young, J.M., Tseng, L.J. and van den Ende, G. (2007b) Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J Urol* 177: 1071–7.
- Michel, M.C. and Vrydag, W. (2006) Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol* 147: S88–119.
- Mongin, G. (2007) Tramadol extended-release formulations in the management of pain due to osteoarthritis. *Expert Rev Neurother* 7: 1775–84.
- Morelli, A., Vignozzi, L., Filippi, S., Vannelli, G.B., Ambrosini, S., Mancina, R. *et al.* (2007) BXL-628, a vitamin D receptor agonist effective in benign prostatic hyperplasia treatment, prevents RhoA activation and inhibits RhoA/Rho kinase signaling in rat and human bladder. *Prostate* 67: 234–47.
- Morita, T., Iizuka, H., Iwata, T. and Kondo, S. (2000) Function and distribution of beta3-adrenoceptors in rat, rabbit and human urinary bladder and external urethral sphincter. *J Smooth Muscle Res* 36: 21–32.

- Nishiguchi, J., Kwon, D.D., Kaiho, Y., Chancellor, M. B., Kumon, H., Snyder, P.B. *et al.* (2007) Suppression of detrusor overactivity in rats with bladder outlet obstruction by a type 4 phosphodiesterase inhibitor. *BJU Int* 99: 680–6.
- Nomiya, M. and Yamaguchi, O. (2003) A quantitative analysis of mRNA expression of alpha 1 and beta-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. *J Urol* 170: 649–53.
- Novara, G., Galfano, A., Ficarra, V. and Artibani, W. (2006) Anticholinergic drugs in patients with bladder outlet obstruction and lower urinary tract symptoms: A systematic review. *Eur Urol* 50: 675–83.
- Otsuka, A., Shinbo, H., Matsumoto, R., Kurita, Y. and Ozono, S. (2008) Expression and functional role of beta-adrenoceptors in the human urinary bladder urothelium. *Naunyn Schmiedebergs Arch Pharmacol* 377: 473–81.
- Pehrson, R. and Andersson, K.E. (2003) Tramadol inhibits rat detrusor overactivity caused by dopamine receptor stimulation. *J Urol* 170: 272–5.
- Pehrson, R., Stenman, E. and Andersson, K.E. (2003) Effects of tramadol on rat detrusor overactivity induced by experimental cerebral infarction. *Eur Urol* 44: 495–9.
- Peters, S.L., Schmidt, M. and Michel, M.C. (2006) Rho kinase: a target for treating urinary bladder dysfunction? *Trends Pharmacol Sci* 27: 492–7.
- Roehrborn, C.G., Siami, P., Barkin, J., Damião, R., Major-Walker, K., Morrill, B. *et al.* (2008) CombAT Study Group. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *Urol* 2008 179: 616–21.
- Rovner, E.S., Kreder, K., Sussman, D.O., Kaplan, S.A., Carlsson, M., Bavendam, T. and Guan, Z. (2008) Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. *J Urol* 180: 1034–41.
- Ruggieri Sr, M.R., Braverman, A.S. and Pontari, M.A. (2005) Combined use of alpha-adrenergic and muscarinic antagonists for the treatment of voiding dysfunction. *J Urol* 174: 1743–8.
- Sacco, E., Pinto, F. and Bassi, P. (2008) Emerging pharmacological targets in overactive bladder therapy: experimental and clinical evidences. *Int Urogynecol J Pelvic Floor Dysfunct* 19: 583–98.
- Safarinejad, M.R. and Hosseini, S.Y. (2006) Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study. *Br J Clin Pharmacol* 61: 456–63.
- Saffroy, M., Torrens, Y., Glowinski, J. and Beaujouan, J.C. (2003) Autoradiographic distribution of tachykinin NK2 binding sites in the rat brain: comparison with NK1 and NK3 binding sites. *Neuroscience* 116: 761–73.
- Sairam, K., Kulinskaya, E., McNicholas, T.A., Boustead, G.B. and Hanbury, D.C. (2002) Sildenafil influences lower urinary tract symptoms. *BJU Int* 90: 836–9.
- Schröder, A., Colli, E., Maggi, M. and Andersson, K. E. (2006) Effects of a vitamin D3 analogue in a rat model of bladder outflow obstruction. *BJU Int* 98: 637–42.
- Seki, S., Erickson, K.A., Seki, M., Nishizawa, O., Igawa, Y., Ogawa, T. *et al.* (2005) Elimination of rat spinal neurons expressing neurokinin 1 receptors reduces bladder overactivity and spinal c-fos expression induced by bladder irritation. *Am J Physiol Renal Physiol* 288: F466–73.
- Singh, S.K., Agarwal, M.M., Batra, Y.K., Kishore, A.V. and Mandal, A.K. (2008) Effect of lumbar-epidural administration of tramadol on lower urinary tract function. *Neurourol Urodyn* 27: 65–70.
- Steers, W.D., Herschorn, S., Kreder, K.J., Moore, K., Strohbehn, K., Yalcin, I. *et al.* (2007) Duloxetine OAB Study Group. Duloxetine compared with placebo for treating women with symptoms of overactive bladder. *BJU Int* 100: 337–45.
- Stief, C.G., Porst, H., Neuser, D., Beneke, M. and Ulbrich, E. (2008) A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol* 53: 1236–44.
- Streng, T., Axelsson, H.E., Hedlund, P., Andersson, D.A., Jordt, S.E., Bevan, S. *et al.* (2008) Distribution and function of the hydrogen sulfide-sensitive TRPA1 ion channel in rat urinary bladder. *Eur Urol* 53: 391–9.
- Striano, P. and Striano, S. (2008) Gabapentin: a Ca²⁺ channel alpha 2-delta ligand far beyond epilepsy therapy. *Drugs Today (Barc)* 44: 353–68.
- Takeda, M., Obara, K., Mizusawa, T., Tomita, Y., Arai, K., Tsutsui, T. *et al.* (1999) Evidence for beta3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. *J Pharmacol Exp Ther* 288: 1367–73.
- Takasu, T., Ukai, M., Sato, S., Matsui, T., Nagase, I., Maruyama, T. *et al.* (2007) Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther* 321: 642–7.
- Takeda, H., Yamazaki, Y., Igawa, Y., Kaidoh, K., Akahane, S., Miyata, H. *et al.* (2002) Effects of beta(3)-adrenoceptor stimulation on prostaglandin E(2)-induced bladder hyperactivity and on the cardiovascular system in conscious rats. *Neurourol Urodyn* 21: 558–65.

Truss, M.C., Stief, C.G., Uckert, S., Becker, A.J., Schultheiss, D., Machtens, S. *et al.* (2000) Initial clinical experience with the selective phosphodiesterase-I isoenzyme inhibitor vinpocetine in the treatment of urge incontinence and low compliance bladder. *World J Urol* 18: 439–443.

Truss, M.C., Stief, C.G., Uckert, S., Becker, A.J., Wefer, J., Schultheiss, D. *et al.* (2001) Phosphodiesterase 1 inhibition in the treatment of lower urinary tract dysfunction: from bench to bedside. *World J Urol* 19: 344–350.

Uchida, H., Shishido, K., Nomiya, M. and Yamaguchi, O. (2005) Involvement of cyclic AMP-dependent and -independent mechanisms in the relaxation of rat detrusor

muscle via beta-adrenoceptors. *Eur J Pharmacol* 518: 195–202.

Uckert, S., Kuthe, A., Jonas, U. and Stief, C.G. (2001) Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. *J Urol* 166: 2484–90.

Woods, M., Carson, N., Norton, N.W., Sheldon, J.H. and Argentieri, T.M. (2001) Efficacy of the beta3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. *J Urol* 166: 1142–7.

Yoshimura, N., Kaiho, Y., Miyazato, M., Yunoki, T., Tai, C., Chancellor, M.B. *et al.* (2008) Therapeutic receptor targets for lower urinary tract dysfunction. *Naunyn Schmiedebergs Arch Pharmacol* 377: 437–48.

Visit SAGE journals online
<http://tau.sagepub.com>

SAGE JOURNAL
Online