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Bladder Pharmacology and Treatment of Lower Urinary Tract Symptoms: Recent Advances

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INTRODUCTION

According to the International Continence Society (ICS), Lower Urinary Tract Symptoms (LUTS) can be divided into three groups: storage symptoms, voiding symptoms, and post micturition symptoms [1]. The term LUTS was originally introduced to separate male urinary symptoms from any implied symptom origin, such as the prostate [2]. LUTS in men typically occur in association with bladder outlet obstruction (BOO) secondary to benign prostatic hyperplasia (BPH); however, the two conditions do not invariably coexist. Thus, male LUTS might be due neither to BOO nor prostatic disease.

The prevalence of LUTS seems to be similar in women and men [3], with nocturia being the most prevalent symptom (48.6% in men; 54.5% in women). The prevalence of storage LUTS (51.3% in men; 59.2% in women) was greater than that of voiding (25.7% in men; 19.5% in women) and postmicturition (16.9% in men; 14.2% in women) symptoms combined [3]. In women, LUTS are usually equal to overactive bladder (OAB) syndrome and are assumed to be caused by detrusor overactivity (DO), even if this does not always appear to be the case [4-7]. Irwin *et al.* (2006) studied 19,000 adult men and women and confirmed that OAB is not solely a female disorder. They found that the prevalence in both sexes is around 12% and that the rate increases with age. They also found that the prevalence of storage LUTS (suggestive of OAB) was twice as common in men as voiding LUTS.

Available information thus suggests that LUTS are a group of non-sex-specific and non-organ-specific symptoms, which are sometimes age-related and progressive. A broader clinical perspective has been advocated: all LUTS should be treated, not just selected symptoms [8].

Concerning pathophysiology of storage symptoms in men, focus has shifted from the prostate to the bladder as the source of some of the LUTS and as the therapeutic target [9-11]. This has created a renewed interest in OAB drugs for treatment of male LUTS and has opened the door for new combinations of drugs. Such combinations are being evaluated in clinical trials [12-15] and seem to be increasingly prescribed "off label" by physicians. Still, there is a need for more effective treatments.

Since the pathophysiology of LUTS/OAB is multifactorial [16], there are many potential targets for future drugs, as identified in preclinical investigations [17,18]. However, it is difficult to predict what principles can be applied clinically. The mere finding that a drug affects the LUT in a desirable direction seldom motivates speculations like "this may be a new way of treating LUTS/OAB". For several of the potentially useful drugs, published clinical studies have demonstrated the proof of principle. This review will discuss the pharmacology of and clinical experiences with some of these drugs.

SUBTYPE SELECTIVE α_1-ADRENOCEPTOR ANTAGONISTS

Currently used α_1-adrenoceptor (AR) antagonists are effective for treatment of both storage and voiding LUTS associated with or suggestive of BPH [19,20]. However, in females with OAB, α1-AR antagonists seem to be ineffective. In a randomized controlled trial (RCT) comprising 364 women with OAB, no effect of tamsulosin versus placebo could be demonstrated [21]. On the other hand, voiding symptoms in women with functional outflow obstruction or LUTS were successfully treated with an α_1-AR antagonist [22,23].

The main question is if better efficacy and/or tolerability can be obtained by highly subtype selective drugs than with the

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commonly used alternatives. Is selectivity for α_1A-, α_1D-, or α_1A/D -ARs the most favorable? Selectivity for α_1B-AR has been considered disadvantageous from a cardiovascular point of view [24,25].

In males, it has been assumed that the targets for α_1-AR antagonists were to be found in the prostate and other parts of the LUT. Kojima *et al*. (2004) studied the expression of α_1-AR in the transitional zone of 28 prostates with BPH. Twelve (43%) were α_1A-AR dominant, whereas 16 (57%) were α_1D-AR dominant. The implications of these findings to the selection of α_1-AR antagonist were further investigated using naftopidil and claimed to antagonize preferably α_1D-ARs. In apparent agreement with the *in vitro* findings, naftopidil was shown to provide significant advantage in the treatment of α_1D-AR dominant BPH patients [26]. However, the selectivity of naftopidil for α_1D- vs α_1A-ARs is modest [27], and its use as a tool to separate between α_1-AR subtypes is questionable (see below).

A previous studies had shown that targeting the predominant α_1-AR (α_1A/L) in the prostate did not result in more effective drugs [28]. However, silodosin (KD-3213), which has a high selectivity for α_1A-ARs [29,30], had clinically good effects on both voiding and storage symptoms [31,32], even if treatment was associated with a high incidence of ejaculatory dysfunction. It thus seems as if selective blockade of α_1A-ARs is a clinically effective approach.

Interest has been focussed on the α_1-ARs (α_1D), specifically in the bladder [24,25], assuming that these receptors were responsible for storage symptoms. The inter-relationship between the α_1D-ARs in the human detrusor smooth muscle and the pathophysiology of LUTS is unclear. However, α_1D-ARs may have effects on different locations in the bladder beside the detrusor smooth muscle: the detrusor vasculature, the urothelium, the afferent and efferent nerve terminals, and the intramural ganglia [33]. Ikemoto *et al.* (2003) gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the I-PSS for storage symptoms, tamsulosin monotherapy decreased the I-PSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α_1-AR subtypes between the drugs) could not be reproduced in a randomized, head-to-head comparison between the drugs [35]. Based on available evidence, it therefore cannot be concluded that the α_1D-ARs on the detrusor smooth muscle are the main therapeutic target. This does not exclude that α_1D-ARs located elsewhere in the bladder, e.g., the vasculature [36] or other structures, might be of importance.

Whether or not α_1-ARs in other structures than the LUT smooth muscles can be targets for the clinically commonly α_1-AR antagonists has still not been established. However, animal experiments clearly suggest that α_1-ARs within the CNS may be important drug targets. In spontanenously hypertensive rats, a well established model of DO, Persson *et al.* (1998) showed that intrathecal, but not intravenous, administration of prazosin (a non-subtype selective α_1-AR antagonist) normalized bladder activity. Sugaya *et al.* (2002) investigated the effects of intrathecal tamsulosin (blocking α_1A/D ARs) and naftopidil (claimed to block preferably the α_1D ARs) on isovolumetric bladder contractions in rats. Intrathecal injection of tamsulosin or naftopidil transiently abolished these contractions. The amplitude of contraction was decreased by naftopidil, but not by tamsulosin. It was speculated that in addition to the antagonistic action of these agents on the α_1A-ARs of prostatic smooth muscle, both agents (especially naftopidil) may also act on the lumbosacral cord (α_1D-ARs).

Taken together, it seems that besides using the non-subtype selective α_1-AR antagonists, selective targeting of either α_1A- (silodosin) or α_1A/D-ARs (tamsulosin, naftopidil) are clinically effective approaches. In the absence of clinically available drugs with a high selectivity for α1D-ARs, the importance of this receptor subtype remains unclear. Considering, the high frequency of ejaculatory dysfunction with silodosin [39], drugs with a higher (compared to presently available drugs) but balanced selectivity for α_1A/D-AR over α_1B-ARs, may be the best option for treatment of male LUTS/OAB.

β_3-AR AGONISTS

The detrusor muscle containing β-ARs and three subtypes (β_1, β_2, and β_3) have been identified in most species [40,41]. However, the human urothelium also contains all three receptor subtypes [42]. Studies using real-time RT-PCR have revealed a predominant expression of β_3-AR mRNA in human detrusor muscle [41,43], and the functional evidence for an important role in both normal and neurogenic bladders is convincing [41,44-51]. The human detrusor also contains β_2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in this structure [40,41].

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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 BKca channels, may be more important in β-AR mediated relaxation than cAMP [52-55].

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated [42,56]. Murakami *et al.* (2007) found that the relaxation responses of the detrusor were not influenced by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka *et al.* (2008). However, to what extent a urothelial signaling pathway contributes *in vitro* and *in vivo* to the relaxant effects of β-AR agonists in general, and β_3-AR agonists specifically, remains to be elucidated.

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 the residual volume [44,57-59]. 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 [61]. 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 controlled clinical trial with this drug in patients with OAB. Tolterodine and placebo served as controls. 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. However, to show that this class of drugs offers a viable therapeutic alternative or complement to current treatment of LUTS/OAB requires further well designed RCTs.

PHOSPHODIESTERASE (PDE) INHIBITORS

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [40,64]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [40]. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach [33]. There are presently 11 families of PDEs, some of which preferentially hydrolyse either cAMP or cGMP [33].

As a basis for PDE inhibitor treatment of LUTS, Uckert *et al.* (2001) investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. *In vitro*, human detrusor muscle responded poorly to sodium nitroprusside and to agents acting via the cGMP system [66]. However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone [67]. Significant dose-dependent relaxations were also induced by human cAMP analogs [67]. With these studies as a background, Truss *et al.* (2000) presented preliminary clinical data with vinpocetine in patients with urgency, urgency incontinence, or low compliance bladders not responding to standard antimuscarinic therapy. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine only showed statistically significant results for one parameter [67]. Studies with PDE 1 inhibitors other than vinpocetin (which may not be an optimal drug for elucidating 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 [68] and rat [69,70] bladder strips and also suppressed rhythmic bladder contractions of the isolated guinea pig bladder [71].

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Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose-limiting effect [72]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [73]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita *et al.* (2000) examined the effects of isoproterenol, prostaglandin E1 and E2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström *et al.* (2006) characterized the distribution of PDE 5, cGMP, and PKG1 in female pig and human urethra and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells and also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil, and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations.

The distribution of PDEs in the male urethral structures does not seem to have been studied.

The observation that patients treated for erectile dysfunction with PDE 5 inhibitors had an improvement of their LUTS has sparked a new interest in using these drugs for treatment of LUTS and OAB. After the report in an open study that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS [75], this observation has been confirmed in several well designed and conducted RCTs [77,78].

McVary *et al.* (2007a) evaluated the effects of sildenafil (50-100 mg daily for 12 weeks) on erectile dysfunction and LUTS in men 45 years or older who scored 25 or less on the erectile function domain of the International Index of Erectile Function (IIEF) and 12 or greater on the International Prostate Symptom Score (IPSS). In 189 men receiving sildenafil, significant improvements were observed in IPPS (-6.32 vs -1.93, $p<0.0001$), Benign Prostatic Hyperplasia Impact Index (-2.0 vs -0.9, $p<0.0001$), mean IPSS quality of life score (-0.97 vs -0.29, $p<0.0001$), and total Self-Esteem and Relationship questionnaire scores (24.6 vs 4.3, $p<0.0001$). Interestingly, there was no difference in urinary flow between the groups ($p=0.08$). Significantly more sildenafil versus placebo treated patients were satisfied with treatment (71.2 vs 41.7, $p<0.0001$). Sildenafil was well tolerated.

In a well designed RCT, treatment with tadalafil once daily, in addition to improving erectile function in men with LUTS, was demonstrated to produce a clinically meaningful and statistically significant symptomatic improvement of LUTS [77]. In another RCT, vardenafil given twice daily for eight weeks to men with ED and LUTS and was shown to significantly improve LUTS, erectile function, and quality of life [78].

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In the trials referred to, no such effect was found. 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).

VITAMAN D_3 RECEPTOR ANALOGUES

Rat and human bladders were shown to express receptors for vitamin D [79], which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D3 have also been shown to inhibit BPH cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [80-82]. Experiments in rats with bladder outflow obstruction showed that one of the analogues, BXL-628, at non-hypercalcemic doses did not prevent bladder hypertrophy but reduced the damage to the bladder smooth muscle, which occurs with increasing bladder weight [83]. The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [84]. Upregulation of this pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO [85,86]. The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that BXL628 was able to arrest prostate growth within 12 weeks in men aged 50 years or more with prostatic

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volume greater than or equal to 40 ml [87]. In a RCT enrolling 120 female patients with OAB where the primary endpoint was an increase in the mean volume voided, a significant increase was demonstrated versus placebo [88]. Whether or not vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB requires further RCTs.

GONADOTROPIN-RELEASING HORMONE ANTAGONISTS

The beneficial effects of the 5a-reductase inhibitors (5-ARIs) finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example antiandrogens or gonadotropin-releasing hormone (GNRH; also known as luteinizing hormone-releasing hormone: LHRH) agonists, is either poor or at the expense of unacceptable side effects, such as medical castration associated with hot flashes, decrease of potency and libido, and negative effects on bone density following long-term androgen ablation [89-92]. With LHRH antagonists submaximal, non-castrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus avoiding medical castration.

Debruyne *et al*. (2008) demonstrated in a two phase RCT that the LHRH antagonist cetrorelix, given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS > 13, peak urinary flow rates 5-13 ml/s), rapidly caused a significant improvement in the mean IPSS: the peak decrease was -5.4 to -5.9 vs -2.8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug offered a safe and effective treatment of male LUTS. Further studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

CENTRALLY ACTING DRUGS

Many parts of the brain seem to be activated during storage and voiding [94-96], and there is increasing interest in drugs modulating the micturition reflex by a central action [96]. Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples. However, central nervous mechanisms so far have not been preferred targets for drugs aimed at treating OAB, since selective actions may be difficult to obtain. Holstege, reviewing some of the central mechnisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that "the problem in 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."

GABAPENTIN

Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [98]. It was originally designed as an anticonvulsant GABA (y-aminobutyric acid) mimeticly capable of crossing the blood-brain barrier [99]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [99]. It has been suggested that it acts by binding to a subunit of the α2δ unit of voltage-dependent calcium channels [98,100]. 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 α2δ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives.

TRAMADOL

Tramadol is a well-known analgesic drug [103]. 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 [103]. 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 [104].

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction [105]. Tramadol also inhibited DO induced by apomorphine in rats [106] – a crude model of

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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. In a double-blind, placebo-controlled, randomized study, Safarinejad and Hosseini (2006) evaluated the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100-mg tramadol sustained release every 12 hours for 12 weeks. Clinical evaluation was performed at baseline and every two weeks during treatment. Tramadol significantly reduced the number of incontinence periods and induced significant improvements in urodynamic parameters. The main adverse event was nausea. It was 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 LUTS/OAB, 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) have been demonstrated in various CNS regions, including those involved in micturition control [109-111]. 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 in both normal rats and more clearly in rats with bladder hypertrophy secondary to BOO [112]. Capsaicin-induced detrusor overactivity was reduced by blocking NK1 receptor-expressing neurons in the spinal cord by using the intrathecally-administered substance P-saponin conjugate [113]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [114].

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 [115]. Intracerebroventricular administration of NK1 and NK2 receptor antagonists were used to awake rats' suppressed detrusor activity induced by dopamine receptor (L-DOPA) stimulation [116]. 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 [117] 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 [118]. 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 five 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 [119,120]. 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 [12,13,15,77,121-124]. Speculatively, several other combinations can be suggested [125].

FUTURE DIRECTIONS

Botulinum toxin A and the vanilloid receptor agonists capsaicin and resiniferatoxin are principles with good evidence (RCTs) of therapeutic effect in OAB/DO [17]. Botulinum toxin A, although not approved for use in OAB/DO in most countries, has a well documented therapeutic effect in neurogenic detrusor overactivity, and it may also be useful for IDO. It has largely replaced the vanilloids as therapeutic alternatives

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in patients not responding to antimuscarinic treatment. 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. These 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 models [126]. 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 [127-129]. 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 [130], and intravesical instillation of a TRPV4 agonist in the rat triggered a novel voiding reflex, which could regulate the late phase of contraction [131]. In the conscious ewe, TRPV4 may also be involved in a urethra to bladder reflex, proposed to facilitate bladder emptying [132]. 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. Subtype selective α_1-AR antagonists (α_1A- silodosin), β_3-AR agonists (YM178), PDE 5 inhibitors (sildenafil, tadalafil, vardenafil), vitamin D analogs (elocalcitol), LHRH analogs (cetrorelix), 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.

CORRESPONDENCE

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